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(71) Applicant (*for all designated States except US*): GENOME THERAPEUTICS CORPORATION [US/US]; 100 Beaver Street, Waltham, MA 02453-8443 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CARULLI, John, P. [US/US]; 9 Harris Drive, Southboro, MA 01772 (US). LITTLE, Randall, D. [US/US]; 62A Marshall Street, Needham, MA 02192 (US). RECKER, Robert, R. [US/US]; 3309 South 116th Street, Omaha, NE 68144 (US). JOHNSON, Mark, L. [US/US]; 16216 N. Circle, Omaha, NE 68135 (US).

(74) Agents: REA, Teresa, Stanek; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 et al. (US).

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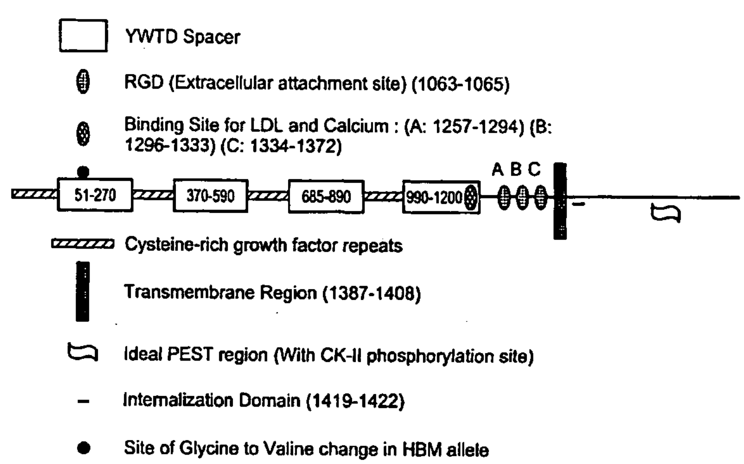
(54) Title: THE HIGH BONE MASS GENE OF 11q13.3

Model for a LDL Receptor-Related protein, Zmax1



(57) Abstract: The present invention relates to methods and materials used to isolate and detect a high bone mass gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The genes identified in the present invention are implicated in bone development and in focal adhesion signaling. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.

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THE HIGH BONE MASS GENE OF 11q13.3

FIELD OF THE INVENTION

The present invention relates generally to the field of genetics, genomics and molecular biology. More particularly, the invention relates to methods and materials used to isolate, detect and sequence a high bone mass gene and corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The genes identified in the present invention are implicated in the ontology and physiology of bone development. The invention also provides nucleic acids, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing, preventing and screening for normal and abnormal conditions of bone, including metabolic bone diseases such as osteoporosis.

BACKGROUND OF THE INVENTION

Two of the most common types of osteoporosis are postmenopausal and senile osteoporosis. Osteoporosis affects men as well as women, and, taken with other abnormalities of bone, presents an ever-increasing health risk for an aging population. The most common type of osteoporosis is that associated with menopause. Most women lose between 20-60% of the bone mass in the trabecular compartment of the bone within 3-6 years after the cessation of menses. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among postmenopausal women. There are an estimated 25 million women in the United States alone who are afflicted with this disease. The results of osteoporosis are both personally

harmful, and also account for a large economic loss due to its chronicity and the need for extensive and long-term support (hospitalization and nursing home care) from the disease sequelae. This is especially true in more elderly patients. Additionally, while osteoporosis is generally not thought of as a life-threatening condition, a 20-30% mortality rate is related to hip fractures in elderly women. A large percentage of this mortality rate can be directly associated with postmenopausal osteoporosis.

The most vulnerable tissue in the bone to the effects of postmenopausal osteoporosis is the trabecular bone. This tissue is often referred to as spongy bone and is particularly concentrated near the ends of the bone near the joints and in the vertebrae of the spine. The trabecular tissue is characterized by small structures which inter-connect with each other as well as the more solid and dense cortical tissue which makes up the outer surface and central shaft of the bone. This criss-cross network of trabeculae gives lateral support to the outer cortical structure and is critical to the biomechanical strength of the overall structure. In postmenopausal osteoporosis, it is primarily the net resorption and loss of the trabeculae which lead to the failure and fracture of the bone. In light of the loss of the trabeculae in postmenopausal women, it is not surprising that the most common fractures are those associated with bones which are highly dependent on trabecular support, e.g., the vertebrae, the neck of the femur, and the forearm. Indeed, hip fracture, Colle's fractures, and vertebral crush fractures are indicative of postmenopausal osteoporosis.

One of the earliest generally accepted methods for treatment of postmenopausal osteoporosis was estrogen replacement therapy. Although this therapy frequently is successful, patient compliance is low, primarily due to the undesirable side-effects of chronic estrogen treatment. Frequently cited side-effects of estrogen replacement therapy include reinitiation of menses, bloating, depression, and fear of breast or uterine cancer. In order to limit the known threat of uterine cancer in those women who have not undergone a hysterectomy, a protocol of

estrogen and progestin cyclic therapy is often employed. This protocol is similar to that which is used in birth control regimens, and often is not tolerated by women because of the side-effects characteristic of progestin. More recently, certain antiestrogens, originally developed for the treatment of breast cancer, have been shown in experimental models of postmenopausal osteoporosis to be efficacious. Among these agents is raloxifene (See, U.S. Patent No. 5,393,763, and Black et al, *J. Clin. Invest.,* 93:63-69 (1994)). In addition, tamoxifene, a widely used clinical agent for the treatment of breast cancer, has been shown to increase bone mineral density in post menopausal women suffering from breast cancer (Love et al, *N. Engl. J. Med.*, 326:852-856 (1992)).

Another therapy for the treatment of postmenopausal osteoporosis is the use of calcitonin. Calcitonin is a naturally occurring peptide which inhibits bone resorption and has been approved for this use in many countries (Overgaard et al, *Br. Med. J.*, 305:556-561 (1992)). The use of calcitonin has been somewhat limited, however. Its effects are very modest in increasing bone mineral density and the treatment is very expensive. Another therapy for the treatment of postmenopausal osteoporosis is the use of bis-phosphonates. These compounds were originally developed for use in Paget's disease and malignant hypercalcemia. They have been shown to inhibit bone resorption. Alendronate, one compound of this class, has been approved for the treatment of postmenopausal osteoporosis. These agents may be helpful in the treatment of osteoporosis, but these agents also have potential liabilities which include osteomalacia, extremely long half-life in bone (greater than 2 years), and possible "frozen bone syndrome," e.g., the cessation of normal bone remodeling.

Senile osteoporosis is similar to postmenopausal osteoporosis in that it is marked by the loss of bone mineral density and resulting increase in fracture rate, morbidity, and associated mortality. Generally, it occurs in later life, i.e., after 70 years of age. Historically, senile osteoporosis has been more common in females, but with the advent of a more elderly male population, this disease is becoming a

major factor in the health of both sexes. It is not clear what, if any, role hormones such as testosterone or estrogen have in this disease, and its etiology remains obscure. Treatment of this disease has not been very satisfactory. Hormone therapy, estrogen in women and testosterone in men, has shown equivocal results; calcitonin and bis-phosphonates may be of some utility.

The peak mass of the skeleton at maturity is largely under genetic control. Twin studies have shown that the variance in bone mass between adult monozygotic twins is smaller than between dizygotic twins (Slemenda et al, *J. Bone Miner. Res.*, 6:561-567 (1991); Young et al, *J. Bone Miner. Res.*, 6:561-567 (1995); Pocock et al, *J. Clin. Invest.*, 80:706-710 (1987); Kelly et al, *J. Bone Miner. Res.*, 8:11-17 (1993)), and it has been estimated that up to 60% or more of the variance in skeletal mass is inherited (Krall et al, *J. Bone Miner. Res.*, 10:S367 (1993)). Peak skeletal mass is the most powerful determinant of bone mass in elderly years (Hui et al, *Ann. Int. Med.*, 111:355-361 (1989)), even though the rate of age-related bone loss in adult and later life is also a strong determinant (Hui et al, *Osteoporosis Int.*, 1:30-34 (1995)). Since bone mass is the principal measurable determinant of fracture risk, the inherited peak skeletal mass achieved at maturity is an important determinant of an individual's risk of fracture later in life. Thus, study of the genetic basis of bone mass is of considerable interest in the etiology of fractures due to osteoporosis.

Recently, a strong interest in the genetic control of peak bone mass has developed in the field of osteoporosis. The interest has focused mainly on candidate genes with suitable polymorphisms to test for association with variation in bone mass within the normal range, or has focused on examination of genes and gene loci associated with low bone mass in the range found in patients with osteoporosis. The vitamin D receptor locus (VDR) (Morrison et al, *Nature*, 367:284-287 (1994)), PTH gene (Howard et al, *J. Clin. Endocrinol. Metab.*, 80:2800-2805 (1995); Johnson et al, *J. Bone Miner. Res.*, 8:11-17 (1995); Gong et al, *J. Bone Miner. Res.*, 10:S462 (1995)) and the estrogen receptor gene (Hosoi et al, *J. Bone Miner. Res.*, 10:S170 (1995); Morrison et al, *Nature*, 367:284-287 (1994)) have figured most prominently

in this work. These studies are difficult because bone mass (the phenotype) is a continuous, quantitative, polygenic trait, and is confounded by environmental factors such as nutrition, co-morbid disease, age, physical activity, and other factors. Also, this type of study design requires large numbers of subjects. In particular, the results of VDR studies to date have been confusing and contradictory (Garnero et al, *J. Bone Miner. Res.*, 10:1283-1288 (1995); Eisman et al, *J. Bone. Miner. Res.*, 10:1289-1293 (1995); Peacock, *J. Bone Miner. Res.*, 10:1294-1297 (1995)). Furthermore, the work thus far has not shed much light on the mechanism(s) whereby the genetic influences might exert their effect on bone mass.

While it is well known that peak bone mass is largely determined by genetic rather than environmental factors, studies to determine the gene loci (and ultimately the genes) linked to variation in bone mass are difficult and expensive. Study designs which utilize the power of linkage analysis, e.g., sib-pair or extended family, are generally more informative than simple association studies, although the latter do have value. However, genetic linkage studies involving bone mass are hampered by two major problems. The first problem is the phenotype, as discussed briefly above. Bone mass is a continuous, quantitative trait, and establishing a discrete phenotype is difficult. Each anatomical site for measurement may be influenced by several genes, many of which may be different from site to site. The second problem is the age component of the phenotype. By the time an individual can be identified as having low bone mass, there is a high probability that their parents or other members of prior generations will be deceased and therefore unavailable for study, and younger generations may not have even reached peak bone mass, making their phenotyping uncertain for genetic analysis.

Regardless, linkage analysis can be used to find the location of a gene causing a hereditary "disorder" and does not require any knowledge of the biochemical nature of the disorder, i.e., a mutated protein that is believed to cause the disorder does not need to be known. Traditional approaches depend on assumptions concerning the disease process that might implicate a known protein as

a candidate to be evaluated. The genetic localization approach using linkage analysis can be used to first find the general chromosomal region in which the defective gene is located and then to gradually reduce the size of the region in order to determine the location of the specific mutated gene as precisely as possible. After the gene itself is discovered within the candidate region, the messenger RNA and the protein are identified and, along with the DNA, are checked for mutations.

The genetic localization approach has practical implications since the location of the disease can be used for prenatal diagnosis even before the altered gene that causes the disease is found. Linkage analysis can enable families, even many of those that do not have a sick child, to know whether they are carriers of a disease gene and to evaluate the condition of an unborn child through molecular diagnosis. The transmission of a disease within families, then, can be used to find the defective gene. As used herein, reference to "high bone mass" (HBM) is analogous to reference to a disease state, although from a practical standpoint high bone mass can actually help a subject avoid the disease known as osteoporosis.

Linkage analysis is possible because of the nature of inheritance of chromosomes from parents to offspring. During meiosis, the two parental homologues pair to guide their proper separation to daughter cells. While they are lined up and paired, the two homologues exchange pieces of the chromosomes, in an event called "crossing over" or "recombination." The resulting chromosomes are chimeric, that is, they contain parts that originate from both parental homologues. The closer together two sequences are on the chromosome, the less likely that a recombination event will occur between them, and the more closely linked they are. In a linkage analysis experiment, two positions on the chromosomes are followed from one generation to the next to determine the frequency of recombination between them. In a study of an inherited disease, one of the chromosomal positions is marked by the disease gene or its normal counterpart, i.e., the inheritance of the chromosomal region can be determined by examining whether the individual displays symptoms of the disorder or not. The other position is marked by a DNA

sequence that shows natural variation in the population such that the two homologues can be distinguished based on the copy of the "marker" sequence that they possess. In every family, the inheritance of the genetic marker sequence is compared to the inheritance of the disease state. If, within a family carrying an autosomal dominant disorder such as high bone mass, every affected individual carries the same form of the marker and all the unaffected individuals carry at least one different form of the marker, there is a great probability that the disease gene and the marker are located close to each other. In this way, chromosomes may be systematically checked with known markers and compared to the disease state. The data obtained from the different families is combined, and analyzed together by a computer using statistical methods. The result is information indicating the probability of linkage between the genetic marker and the disease allowing different distances between them. A positive result can mean that the disease is very close to the marker, while a negative result indicates that it is far away on that chromosome, or on an entirely different chromosome.

Linkage analysis is performed by typing all members of the affected family at a given marker locus and evaluating the co-inheritance of a particular disease state with the marker probe, thereby determining how often the two of them are co-inherited. The recombination frequency can be used as a measure of the genetic distance between two gene loci. A recombination frequency of 1% is equivalent to 1 map unit, or 1 centiMorgan (cM), which is roughly equivalent to 1,000 kb of DNA. This relationship holds up to frequencies of about 20% or 20 cM.

The entire human genome is 3,300 cM long. In order to find an unknown disease gene within 5-10 cM of a marker locus, the whole human genome can be searched with roughly 330 informative marker loci spaced at approximately 10 cM intervals (Botstein et al, *Am. J. Hum. Genet.*, 32:314-331 (1980)). The reliability of linkage results is established by using a number of statistical methods. The method most commonly used for the analysis of linkage in humans is the LOD score method (Morton, *Prog. Clin. Biol. Res.*, 147:245-265 (1984), Morton et al, *Am. J. Hum.*

Genet., 38:868-883 (1986)) which was incorporated into the computer program LIPED by Ott, *Am. J. Hum. Genet.*, 28:528-529 (1976). LOD scores are the logarithm of the ratio of the likelihood that two loci are linked at a given distance to that they are not linked (>50 cM apart). The advantage of using logarithmic values is that they can be summed among families with the same disease. This becomes necessary given the relatively small size of human families.

By convention, a total LOD score greater than + 3.0 (that is, odds of linkage at the specified recombination frequency being 1000 times greater than odds of no linkage) is considered to be significant evidence for linkage at that particular recombination frequency. A total LOD score of less than - 2.0 (that is, odds of no linkage being 100 times greater than odds of linkage at the specified frequency) is considered to be strong evidence that the two loci under consideration are not linked at that particular recombination frequency. Until recently, most linkage analyses have been performed on the basis of two-point data, which is the relationship between the disorder under consideration and a particular genetic marker. However, as a result of the rapid advances in mapping the human genome over the last few years, and concomitant improvements in computer methodology, it has become feasible to carry out linkage analyses using multi-point data. Multi-point analysis provide a simultaneous analysis of linkage between the disease and several linked genetic markers, when the recombination distance among the markers is known.

Multi-point analysis is advantageous for two reasons. First, the informativeness of the pedigree is usually increased. Each pedigree has a certain amount of potential information, dependent on the number of parents heterozygous for the marker loci and the number of affected individuals in the family. However, few markers are sufficiently polymorphic as to be informative in all those individuals. If multiple markers are considered simultaneously, then the probability of an individual being heterozygous for at least one of the markers is greatly increased. Second, an indication of the position of the disease gene among the markers may be determined. This allows identification of flanking markers, and thus

eventually allows isolation of a small region in which the disease gene resides. Lathrop et al, *Proc. Natl. Acad. Sci. USA*, 81:3443-3446 (1984) have written the most widely used computer package, LINKAGE, for multi-point analysis.

There is a need in the art for identifying the gene associated with a high bone mass phenotype. The present invention is directed to this, as well as other, important ends.

SUMMARY OF THE INVENTION

The present invention describes the Zmax1 gene and the HBM gene on chromosome 11q13.3 by genetic linkage and mutation analysis. The use of additional genetic markers linked to the genes has aided this discovery. By using linkage analysis and mutation analysis, persons predisposed to HBM may be readily identified. Cloning methods using Bacterial Artificial Chromosomes have enabled the inventors to focus on the chromosome region of 11q13.3 and to accelerate the sequencing of the autosomal dominant gene. In addition, the invention identifies the Zmax1 gene and the HBM gene, and identifies the guanine-to-thymine polymorphism mutation at position 582 in the Zmax1 gene that produces the HBM gene and the HBM phenotype.

The present invention identifies the Zmax1 gene and the HBM gene, which can be used to determine if people are predisposed to HBM and, therefore, not susceptible to diseases characterized by reduced bone density, including, for example, osteoporosis, or are predisposed and susceptible to diseases characterized by abnormally high bone density, such as, for example, osteoporosis. Older individuals carrying the HBM gene express the HBM protein, and, therefore, do not develop osteoporosis. In other words, the HBM gene is a suppressor of osteoporosis. This *in vivo* observation is a strong evidence that treatment of normal individuals with the HBM gene or protein, or fragments thereof, will ameliorate osteoporosis.

Moreover, such treatment will be indicated in the treatment of bone lesions, particularly bone fractures, for bone remodeling in the healing of such lesions. For example, persons predisposed to or suffering from stress fractures (i.e., the accumulation of stress-induced microfractures, eventually resulting in a true fracture through the bone cortex) may be identified and/or treated by means of the invention. Moreover, the methods and compositions of the invention will be of use in the treatment of secondary osteoporosis, where the course of therapy involves bone remodeling, such as endocrine conditions accompanying corticosteroid administration, hyperthyroidism, hypogonadism, hematologic malignancies, malabsorption and alcoholism, as well as disorders associated with vitamin D and/or phosphate metabolism, such as osteomalacia and rickets, and diseases characterized by abnormal or disordered bone remodeling, such as Paget's disease, and in neoplasms of bone, which may be benign or malignant.

In various embodiments, the present invention is directed to nucleic acids, proteins, vectors, and transformed hosts of HBM and Zmax1.

Additionally, the present invention is directed to applications of the above embodiments of the invention including, for example, gene therapy, pharmaceutical development, and diagnostic assays for bone development disorders. In preferred embodiments, the present invention is directed to methods for treating, diagnosing, preventing and screening for osteoporosis.

These and other aspects of the present invention are described in more detail below.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 shows the pedigree of the individuals used in the genetic linkage studies. Under each individual is an ID number, the z-score for spinal BMD, and the allele calls for the critical markers on chromosome 11. Solid symbols represent "affected" individuals. Symbols containing "N" are "unaffected" individuals. DNA

from 37 individuals was genotyped. Question marks denote unknown genotypes or individuals who were not genotyped.

Fig. 2 depicts the BAC/STS content physical map of the HBM region in 11q13.3. STS markers derived from genes, ESTs, microsatellites, random sequences, and BAC endsequences are denoted above the long horizontal line. For markers that are present in GDB the same nomenclature has been used. Locus names (D11S####) are listed in parentheses after the primary name if available. STSs derived from BAC endsequences are listed with the BAC name first followed by L or R for the left and right end of the clone, respectively. The two large arrows indicate the genetic markers that define the HBM critical region. The horizontal lines below the STSs indicate BAC clones identified by PCR-based screening of a nine-fold coverage BAC library. Open circles indicate that the marker did not amplify the corresponding BAC library address during library screening. Clone names use the following convention: B for BAC, the plate, row and column address, followed by -H indicating the HBM project (i.e., B36F16-H).

Figs. 3A-3F show the genomic structure of Zmax1 with flanking intron sequences. Translation is initiated by the underlined "ATG" in exon 1. The site of the polymorphism in the HBM gene is in exon 3 and is represented by the underlined "G," whereby this nucleotide is a "T" in the HBM gene. The 3' untranslated region of the mRNA is underlined within exon 23 (exon 1, SEQ ID NO:40; exon 2, SEQ ID NO:41; exon 3, SEQ ID NO:42; exon 4, SEQ ID NO:43; exon 5, SEQ ID NO:44; exon 6, SEQ ID NO:45; exon 7, SEQ ID NO:46; exon 8, SEQ ID NO:47; exon 9, SEQ ID NO:48; exon 10, SEQ ID NO:49; exon 11, SEQ ID NO:50; exon 12, SEQ ID NO:51; exon 13, SEQ ID NO:52; exon 14, SEQ ID NO:53; exon 15, SEQ ID NO:54; exon 16, SEQ ID NO:55; exon 17, SEQ ID NO:56; exon 18, SEQ ID NO:57; exon 19, SEQ ID NO:58; exon 20, SEQ ID NO:59; exon 21, SEQ ID NO:60; exon 22, SEQ ID NO:61; and exon 23; SEQ ID NO:62).

Fig. 4 shows the domain organization of Zmax1, including the YWTD spacers, the extracellular attachment site, the binding site for LDL and calcium, the cysteine-rich growth factor repeats, the transmembrane region, the ideal PEST region with the CK-II phosphorylation site and the internalization domain. **Fig. 4** also shows the site of the glycine to valine change that occurs in the HBM protein. The signal peptide is located at amino acids 1-22, the extracellular domain is located at amino acids 23-1385, the transmembrane segment is located at amino acids 1386-1413, and the cytoplasmic domain is located at amino acids 1414-1615.

Fig. 5 is a schematic illustration of the BAC contigs B527D12 and B200E21 in relation to the HBM gene.

Figs. 6A-6E are the nucleotide and amino acid sequences of the wild-type gene, Zmax1. The location for the base pair substitution at nucleotide 582, a guanine to thymine, is underlined. This allelic variant is the HBM gene. The HBM gene encodes for a protein with an amino acid substitution of glycine to valine at position 171. The 5' untranslated region (UTR) boundaries bases 1 to 70, and the 3' UTR boundaries bases 4916-5120.

Figs. 7A and **7B** are northern blot analyses showing the expression of Zmax1 in various tissues.

Fig. 8 is a PCR product analysis.

Fig. 9 is allele specific oligonucleotide detection of the Zmax1 exon 3 mutation.

Fig. 10 is the cellular localization of mouse Zmax1 by *in situ* hybridization at 100X magnification using sense and antisense probes.

Fig. 11 is the cellular localization of mouse Zmax1 by *in situ* hybridization at 400X magnification using sense and antisense probes.

Fig. 12 is the cellular localization of mouse Zmax1 by *in situ* hybridization of osteoblasts in the endosteum at 400X magnification using sense and antisense probes.

Fig. 13 shows antisense inhibition of Zmax1 expression in MC-3T3 cells.

Fig. 14 shows a Zmax1 Exon3 Allele Specific Oligonucleotide (ASO) assay which illustrates the rarity of the HBM1 allele (right panels; T-specific oligo; 58°C Wash) as compared to the wild-type Zmax1 allele (left panels, G-specific oligo; 55°C Wash). The positive spots appearing in the right panels were positive controls.

Fig. 15 depicts a model representing the potential role of Zmax1 in focal adhesion signaling.

DETAILED DESCRIPTION OF THE INVENTION

To aid in the understanding of the specification and claims, the following definitions are provided.

"Gene" refers to a DNA sequence that encodes through its template or messenger RNA a sequence of amino acids characteristic of a specific peptide. The term "gene" includes intervening, non-coding regions, as well as regulatory regions, and can include 5' and 3' ends.

"Gene sequence" refers to a DNA molecule, including both a DNA molecule which contains a non-transcribed or non-translated sequence. The term is also intended to include any combination of gene(s), gene fragment(s), non-transcribed sequence(s) or non-translated sequence(s) which are present on the same DNA molecule.

The sequences of the present invention may be derived from a variety of sources including DNA, cDNA, synthetic DNA, synthetic RNA or combinations thereof. Such sequences may comprise genomic DNA which may or may not include naturally occurring introns. Moreover, such genomic DNA may be obtained in association with promoter regions or poly (A) sequences. The sequences, genomic DNA or cDNA may be obtained in any of several ways. Genomic DNA can be extracted and purified from suitable cells by means well known in the art. Alternatively, mRNA can be isolated from a cell and used to produce cDNA by reverse transcription or other means.

"cDNA" refers to complementary or copy DNA produced from an RNA template by the action of RNA-dependent DNA polymerase (reverse transcriptase). Thus, a "cDNA clone" means a duplex DNA sequence complementary to an RNA molecule of interest, carried in a cloning vector or PCR amplified. This term includes genes from which the intervening sequences have been removed.

"Recombinant DNA" means a molecule that has been recombined by *in vitro* splicing cDNA or a genomic DNA sequence.

"Cloning" refers to the use of *in vitro* recombination techniques to insert a particular gene or other DNA sequence into a vector molecule. In order to successfully clone a desired gene, it is necessary to use methods for generating DNA fragments, for joining the fragments to vector molecules, for introducing the composite DNA molecule into a host cell in which it can replicate, and for selecting the clone having the target gene from amongst the recipient host cells.

"cDNA library" refers to a collection of recombinant DNA molecules containing cDNA inserts which together comprise the entire genome of an organism. Such a cDNA library can be prepared by methods known to one skilled in the art and described by, for example, Cowell and Austin, "cDNA Library Protocols," Methods in Molecular Biology (1997). Generally, RNA is first isolated from the cells of an organism from whose genome it is desired to clone a particular gene.

"Cloning vehicle" refers to a plasmid or phage DNA or other DNA sequence which is able to replicate in a host cell. The cloning vehicle is characterized by one or more endonuclease recognition sites at which such DNA sequences may be cut in a determinable fashion without loss of an essential biological function of the DNA, which may contain a marker suitable for use in the identification of transformed cells.

"Expression control sequence" refers to a sequence of nucleotides that control or regulate expression of structural genes when operably linked to those genes. These include, for example, the lac systems, the trp system, major operator and promoter regions of the phage lambda, the control region of fd coat protein and

other sequences known to control the expression of genes in prokaryotic or eukaryotic cells. Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a prokaryotic or eukaryotic host, and may contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements and/or translational initiation and termination sites.

"Expression vehicle" refers to a vehicle or vector similar to a cloning vehicle but which is capable of expressing a gene which has been cloned into it, after transformation into a host. The cloned gene is usually placed under the control of (i.e., operably linked to) an expression control sequence.

"Operator" refers to a DNA sequence capable of interacting with the specific repressor, thereby controlling the transcription of adjacent gene(s).

"Promoter" refers to a DNA sequence that can be recognized by an RNA polymerase. The presence of such a sequence permits the RNA polymerase to bind and initiate transcription of operably linked gene sequences.

"Promoter region" is intended to include the promoter as well as other gene sequences which may be necessary for the initiation of transcription. The presence of a promoter region is sufficient to cause the expression of an operably linked gene sequence.

"Operably linked" means that the promoter controls the initiation of expression of the gene. A promoter is operably linked to a sequence of proximal DNA if upon introduction into a host cell the promoter determines the transcription of the proximal DNA sequence(s) into one or more species of RNA. A promoter is operably linked to a DNA sequence if the promoter is capable of initiating transcription of that DNA sequence.

"Prokaryote" refers to all organisms without a true nucleus, including bacteria.

"Eukaryote" refers to organisms and cells that have a true nucleus, including mammalian cells.

"Host" includes prokaryotes and eukaryotes, such as yeast and filamentous fungi, as well as plant and animal cells. The term includes an organism or cell that is the recipient of a replicable expression vehicle.

"Fragment" of a gene refers to any variant of the gene that possesses the biological activity of that gene.

"Variant" refers to a gene that is substantially similar in structure and biological activity or immunological characteristics to either the entire gene or to a fragment of the gene. Provided that the two genes possess a similar activity, they are considered variant as that term is used herein even if the sequence of amino acid residues is not identical.

"Amplification of nucleic acids" refers to methods such as polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known in the art and described, for example, in U.S. Patent Nos. 4,683,195 and 4,683,202. Reagents and hardware for conducting PCR are commercially available. Primers useful for amplifying sequences from the HBM region are preferably complementary to, and hybridize specifically to sequences in the HBM region or in regions that flank a target region therein. HBM sequences generated by amplification may be sequenced directly. Alternatively, the amplified sequence(s) may be cloned prior to sequence analysis.

"Antibodies" may refer to polyclonal and/or monoclonal antibodies and fragments thereof, and immunologic binding equivalents thereof, that can bind to the HBM proteins and fragments thereof or to nucleic acid sequences from the HBM region, particularly from the HBM locus or a portion thereof. The term antibody is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities. Proteins may be prepared synthetically in a protein synthesizer and coupled to a carrier molecule and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the HBM protein or fragment. Monoclonal antibodies may be made by injecting

mice with the proteins, or fragments thereof. Monoclonal antibodies will be screened by ELISA and tested for specific immunoreactivity with HBM protein or fragments thereof. Harlow et al, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1988). These antibodies will be useful in assays as well as pharmaceuticals.

"HBM" refers to high bone mass.

"HBM protein" refers to a protein that is identical to a Zmax1 protein except that it contains an alteration of glycine 171 to valine. An HBM protein is defined for any organism that encodes a Zmax1 true homologue. For example, a mouse HBM protein refers to the mouse Zmax1 protein having the glycine 170 to valine substitution.

"HBM gene" refers to the genomic DNA sequence found in individuals showing the HBM characteristic or phenotype, where the sequence encodes the protein indicated by SEQ ID NO: 4. The HBM gene and the Zmax1 gene are allelic. The protein encoded by the HBM gene has the property of causing elevated bone mass, while the protein encoded by the Zmax1 gene does not. The HBM gene and the Zmax1 gene differ in that the HBM gene has a thymine at position 582, while the Zmax1 gene has a guanine at position 582. The HBM gene comprises the nucleic acid sequence shown as SEQ ID NO: 2. The HBM gene may also be referred to as an "HBM polymorphism."

"Normal," "wild-type," "unaffected" and "Zmax1" all refer to the genomic DNA sequence that encodes the protein indicated by SEQ ID NO: 3. The Zmax1 gene has a guanine at position 582. The Zmax1 gene comprises the nucleic acid sequence shown as SEQ ID NO: 1. "Normal," "wild-type," "unaffected" and "Zmax1" also refer to allelic variants of the genomic sequence that encodes proteins that do not contribute to elevated bone mass. The Zmax1 gene is common in the human population, while the HBM gene is rare.

"5YWT+EGF" refers to a repeat unit found in the Zmax1 protein, consisting of five YWT repeats followed by an EGF repeat.

"Bone development" generally refers to any process involved in the change of bone over time, including, for example, normal development, changes that occur during disease states, and changes that occur during aging. "Bone development disorder" particularly refers to any disorders in bone development including, for example, changes that occur during disease states and changes that occur during aging. Bone development may be progressive or cyclical in nature. Aspects of bone that may change during development include, for example, mineralization, formation of specific anatomical features, and relative or absolute numbers of various cell types.

"Bone modulation" or "modulation of bone formation" refers to the ability to affect any of the physiological processes involved in bone remodeling, as will be appreciated by one skilled in the art, including, for example, bone resorption and appositional bone growth, by, inter alia, osteoclastic and osteoblastic activity, and may comprise some or all of bone formation and development as used herein.

"Normal bone density" refers to a bone density within two standard deviations of a Z score of 0.

A "Zmax1 system" refers to a purified protein, cell extract, cell, animal, human or any other composition of matter in which Zmax1 is present in a normal or mutant form.

A "surrogate marker" refers to a diagnostic indication, symptom, sign or other feature that can be observed in a cell, tissue, human or animal that is correlated with the HBM gene or elevated bone mass or both, but that is easier to measure than bone density. The general concept of a surrogate marker is well accepted in diagnostic medicine.

The present invention encompasses the Zmax1 gene and Zmax1 protein in the forms indicated by SEQ ID NOS: 1 and 3, respectively, and other closely related variants, as well as the adjacent chromosomal regions of Zmax1 necessary for its accurate expression. In a preferred embodiment, the present invention is directed to at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 1.

The present invention also encompasses the HBM gene and HBM protein in the forms indicated by SEQ ID NO: 2 and 4, respectively, and other closely related variants, as well as the adjacent chromosomal regions of the HBM gene necessary for its accurate expression. In a preferred embodiment, the present invention is directed to at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2. More preferably, the present invention is directed to at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2, wherein one of the 15 contiguous nucleotides is the thymine at nucleotide 582.

The invention also relates to the nucleotide sequence of the Zmax1 gene region, as well as the nucleotide sequence of the HBM gene region. More particularly, a preferred embodiment are the BAC clones containing segments of the Zmax1 gene region B200E21-H and B527D12-H. A preferred embodiment is the nucleotide sequence of the BAC clones consisting of SEQ ID NOS: 5-12.

The invention also concerns the use of the nucleotide sequence to identify DNA probes for the Zmax1 gene and the HBM gene, PCR primers to amplify the Zmax1 gene and the HBM gene, nucleotide polymorphisms in the Zmax1 gene and the HBM gene, and regulatory elements of the Zmax1 gene and the HBM gene.

This invention describes the further localization of the chromosomal location of the Zmax1 gene and HBM gene on chromosome 11q13.3 between genetic markers D11S987 and SNP_CONTIG033-6, as well as the DNA sequences of the Zmax1 gene and the HBM gene. The chromosomal location was refined by the addition of more genetic markers to the mapping panel used to map the gene, and by the extension of the pedigree to include more individuals. The pedigree extension was critical because the new individuals that have been genotyped harbor critical recombination events that narrow the region. To identify genes in the region on 11q13.3, a set of BAC clones containing this chromosomal region was identified. The BAC clones served as a template for genomic DNA sequencing, and also as a reagent for identifying coding sequences by direct cDNA selection. Genomic sequencing and direct cDNA selection were used to characterize more than 1.5

million base pairs of DNA from 11q13.3. The Zmax1 gene was identified within this region and the HBM gene was then discovered after mutational analysis of affected and unaffected individuals.

When a gene has been genetically localized to a specific chromosomal region, the genes in this region can be characterized at the molecular level by a series of steps that include: cloning of the entire region of DNA in a set of overlapping clones (physical mapping), characterization of genes encoded by these clones by a combination of direct cDNA selection, exon trapping and DNA sequencing (gene identification), and identification of mutations in these genes by comparative DNA sequencing of affected and unaffected members of the HBM kindred (mutation analysis).

Physical mapping is accomplished by screening libraries of human DNA cloned in vectors that are propagated in *E. coli* or *S. cereviseae* using PCR assays designed to amplify unique molecular landmarks in the chromosomal region of interest. To generate a physical map of the HBM candidate region, a library of human DNA cloned in Bacterial Artificial Chromosomes (BACs) was screened with a set of Sequence Tagged Site (STS) markers that had been previously mapped to chromosome 11q12-q13 by the efforts of the Human Genome Project.

STSs are unique molecular landmarks in the human genome that can be assayed by PCR. Through the combined efforts of the Human Genome Project, the location of thousands of STSs on the twenty-two autosomes and two sex chromosomes has been determined. For a positional cloning effort, the physical map is tied to the genetic map because the markers used for genetic mapping can also be used as STSs for physical mapping. By screening a BAC library with a combination of STSs derived from genetic markers, genes, and random DNA fragments, a physical map comprised of overlapping clones representing all of the DNA in a chromosomal region of interest can be assembled.

BACs are cloning vectors for large (80 kilobase to 200 kilobase) segments of human or other DNA that are propagated in *E. coli*. To construct a physical map

using BACs, a library of BAC clones is screened so that individual clones harboring the DNA sequence corresponding to a given STS or set of STSs are identified. Throughout most of the human genome, the STS markers are spaced approximately 20 to 50 kilobases apart, so that an individual BAC clone typically contains at least two STS markers. In addition, the BAC libraries that were screened contain enough cloned DNA to cover the human genome six times over. Therefore, an individual STS typically identifies more than one BAC clone. By screening a six-fold coverage BAC library with a series of STS markers spaced approximately 50 kilobases apart, a physical map consisting of a series of overlapping BAC clones, i.e. BAC contigs, can be assembled for any region of the human genome. This map is closely tied to the genetic map because many of the STS markers used to prepare the physical map are also genetic markers.

When constructing a physical map, it often happens that there are gaps in the STS map of the genome that result in the inability to identify BAC clones that are overlapping in a given location. Typically, the physical map is first constructed from a set of STSs that have been identified through the publicly available literature and World Wide Web resources. The initial map consists of several separate BAC contigs that are separated by gaps of unknown molecular distance. To identify BAC clones that fill these gaps, it is necessary to develop new STS markers from the ends of the clones on either side of the gap. This is done by sequencing the terminal 200 to 300 base pairs of the BACs flanking the gap, and developing a PCR assay to amplify a sequence of 100 or more base pairs. If the terminal sequences are demonstrated to be unique within the human genome, then the new STS can be used to screen the BAC library to identify additional BACs that contain the DNA from the gap in the physical map. To assemble a BAC contig that covers a region the size of the HBM candidate region (2,000,000 or more base pairs), it is often necessary to develop new STS markers from the ends of several clones.

After building a BAC contig, this set of overlapping clones serves as a template for identifying the genes encoded in the chromosomal region. Gene

identification can be accomplished by many methods. Three methods are commonly used: (1) a set of BACs selected from the BAC contig to represent the entire chromosomal region can be sequenced, and computational methods can be used to identify all of the genes, (2) the BACs from the BAC contig can be used as a reagent to clone cDNAs corresponding to the genes encoded in the region by a method termed direct cDNA selection, or (3) the BACs from the BAC contig can be used to identify coding sequences by selecting for specific DNA sequence motifs in a procedure called exon trapping. The present invention includes genes identified by the first two methods.

To sequence the entire BAC contig representing the HBM candidate region, a set of BACs was chosen for subcloning into plasmid vectors and subsequent DNA sequencing of these subclones. Since the DNA cloned in the BACs represents genomic DNA, this sequencing is referred to as genomic sequencing to distinguish it from cDNA sequencing. To initiate the genomic sequencing for a chromosomal region of interest, several non-overlapping BAC clones are chosen. DNA for each BAC clone is prepared, and the clones are sheared into random small fragments which are subsequently cloned into standard plasmid vectors such as pUC18. The plasmid clones are then grown to propagate the smaller fragments, and these are the templates for sequencing. To ensure adequate coverage and sequence quality for the BAC DNA sequence, sufficient plasmid clones are sequenced to yield six-fold coverage of the BAC clone. For example, if the BAC is 100 kilobases long, then phagemids are sequenced to yield 600 kilobases of sequence. Since the BAC DNA was randomly sheared prior to cloning in the phagemid vector, the 600 kilobases of raw DNA sequence can be assembled by computational methods into overlapping DNA sequences termed sequence contigs. For the purposes of initial gene identification by computational methods, six-fold coverage of each BAC is sufficient to yield ten to twenty sequence contigs of 1000 base pairs to 20,000 base pairs.

The sequencing strategy employed in this invention was to initially sequence "seed" BACs from the BAC contig in the HBM candidate region. The sequence of the "seed" BACs was then used to identify minimally overlapping BACs from the contig, and these were subsequently sequenced. In this manner, the entire candidate region was sequenced, with several small sequence gaps left in each BAC. This sequence served as the template for computational gene identification. One method for computational gene identification is to compare the sequence of BAC contig to publicly available databases of cDNA and genomic sequences, e.g. unigene, dbEST, genbank. These comparisons are typically done using the BLAST family of computer algorithms and programs (Altschul et al, *J. Mol. Biol.*, 215:403-410 (1990)). The BAC sequence can also be translated into protein sequence, and the protein sequence can be used to search publicly available protein databases, using a version of BLAST designed to analyze protein sequences (Altschul et al, *Nucl. Acids Res.*, 25:3389-3402 (1997)). Another method is to use computer algorithms such as MZEF (Zhang, *Proc. Natl. Acad. Sci.*, 94:565-568 (1997)) and GRAIL (Uberbacher et al, *Methods Enzymol.*, 266:259-281 (1996)), which predict the location of exons in the sequence based on the presence of specific DNA sequence motifs that are common to all exons, as well as the presence of codon usage typical of human protein encoding sequences.

In addition to identifying genes by computational methods, genes were also identified by direct cDNA selection (Del Mastro et al, *Genome Res.* 5(2):185-194 (1995)). In direct cDNA selection, cDNA pools from tissues of interest are prepared, and the BACs from the candidate region are used in a liquid hybridization assay to capture the cDNAs which base pair to coding regions in the BAC. In the methods described herein, the cDNA pools were created from several different tissues by random priming the first strand cDNA from polyA RNA, synthesizing the second strand cDNA by standard methods, and adding linkers to the ends of the cDNA fragments. The linkers are used to amplify the cDNA pools. The BAC clones are used as a template for *in vitro* DNA synthesis to create a biotin labelled

copy of the BAC DNA. The biotin labelled copy of the BAC DNA is then denatured and incubated with an excess of the PCR amplified, linkered cDNA pools which have also been denatured. The BAC DNA and cDNA are allowed to anneal in solution, and heteroduplexes between the BAC and the cDNA are isolated using streptavidin coated magnetic beads. The cDNAs that are captured by the BAC are then amplified using primers complimentary to the linker sequences, and the hybridization/selection process is repeated for a second round. After two rounds of direct cDNA selection, the cDNA fragments are cloned, and a library of these direct selected fragments is created.

The cDNA clones isolated by direct selection are analyzed by two methods. Since a pool of BACs from the HBM candidate region is used to provide the genomic DNA sequence, the cDNAs must be mapped to individual BACs. This is accomplished by arraying the BACs in microtiter dishes, and replicating their DNA in high density grids. Individual cDNA clones are then hybridized to the grid to confirm that they have sequence identity to an individual BAC from the set used for direct selection, and to determine the specific identity of that BAC. cDNA clones that are confirmed to correspond to individual BACs are sequenced. To determine whether the cDNA clones isolated by direct selection share sequence identity or similarity to previously identified genes, the DNA and protein coding sequences are compared to publicly available databases using the BLAST family of programs.

The combination of genomic DNA sequence and cDNA sequence provided by BAC sequencing and by direct cDNA selection yields an initial list of putative genes in the region. The genes in the region were all candidates for the HBM locus. To further characterize each gene, Northern blots were performed to determine the size of the transcript corresponding to each gene, and to determine which putative exons were transcribed together to make an individual gene. For Northern blot analysis of each gene, probes were prepared from direct selected cDNA clones or by PCR amplifying specific fragments from genomic DNA or from the BAC encoding the putative gene of interest. The Northern blots gave information on the size of the

transcript and the tissues in which it was expressed. For transcripts which were not highly expressed, it was sometimes necessary to perform a reverse transcription PCR assay using RNA from the tissues of interest as a template for the reaction.

Gene identification by computational methods and by direct cDNA selection provides unique information about the genes in a region of a chromosome. When genes are identified, then it is possible to examine different individuals for mutations in each gene.

I. Phenotyping using DXA Measurements

Spinal bone mineral content (BMC) and bone mineral density (BMD) measurements performed at Creighton University (Omaha, Nebraska) were made by DXA using a Norland Instruments densitometer (Norland XR2600 Densitometer, Dual Energy X-ray Absorptiometry, DXA). Spinal BMC and BMD at other locations used the machinery available. There are estimated to be 800 DXA machines currently operating in the U.S. Most larger cities have offices or imaging centers which have DXA capabilities, usually a Lunar or Hologic machine. Each location that provided spine BMC and BMD data included copies of the printouts from their machines to provide verification that the regions of interest for measurement of BMD have been chosen appropriately. Complete clinical histories and skeletal radiographs were obtained.

The HBM phenotype is defined by the following criteria: very high spinal BMD; a clinical history devoid of any known high bone mass syndrome; and skeletal radiographs showing a normal shape of the appendicular skeleton.

II. Genotyping of Microsatellite Markers

To narrow the genetic interval to a region smaller than that originally reported by Johnson et al, *Am. J. Hum. Genet.*, 60:1326-1332 (1997), additional microsatellite markers on chromosome 11q12-13 were typed. The new markers included: D11S4191, D11S1883, D11S1785, D11S4113, D11S4136, D11S4139, (Dib, et al, *Nature*, 380:152-154 (1996), FGF3 (Polymeropolous, et al, *Nucl. Acid Res.*, 18:7468 (1990)), as well as GTC_HBM_Marker_1, GTC_HBM_Marker_2,

GTC_HBM_Marker_3, GTC_HBM_Marker_4, GTC_HBM_Marker_5, GTC_HBM_Marker_6, and GTC_HBM_Marker_7 (*See* **Fig. 2**).

Blood (20 ml) was drawn into lavender cap (EDTA containing) tubes by a certified phlebotomist. The blood was stored refrigerated until DNA extraction. DNA has been extracted from blood stored for up to 7 days in the refrigerator without reduction in the quality or quantity of yield. For those subjects that have blood drawn at distant sites, a shipping protocol was successfully used on more than a dozen occasions. Blood samples were shipped by overnight express in a styrofoam container with freezer packs to provide cooling. Lavender cap tubes were placed on individual plastic shipping tubes and then into "zip-lock" biohazard bags. When the samples arrived the next day, they were immediately processed to extract DNA.

The DNA extraction procedure used a kit purchased from Gentra Systems, Inc. (Minneapolis, Minnesota). Briefly, the procedure involved adding 3 volumes of a red blood cell lysis buffer to the whole blood. After incubations for 10 minutes at room temperature, the solution was centrifuged in a Beckman tabletop centrifuge at 2,000 X g for 10 minutes. The white blood cell pellet was resuspended in Cell Lysis Buffer. Once the pellet was completely resuspended and free of cell clumps, the solution was digested with RNase A for 15 minutes at 37°C. Proteins were precipitated by addition of the provided Protein Precipitation Solution and removed by centrifugation. The DNA was precipitated out of the supernatant by addition of isopropanol. This method was simple and fast, requiring only 1-2 hours, and allowed for the processing of dozens of samples simultaneously. The yield of DNA was routinely >8 mg for a 20 ml sample of whole blood and had a MW of >50 kb. DNA was archived by storing coded 50 μg aliquots at -80°C as an ethanol precipitate.

DNA was genotyped using one fluorescently labeled oligonucleotide primer and one unlabeled oligonucleotide primer. Labeled and unlabeled oligonucleotides were obtained from Integrated DNA Technologies, Inc. (Coralville, Iowa). All other

reagents for microsatellite genotyping were purchased from Perkin Elmer-Applied Biosystems, Inc. ("PE-ABI") (Norwalk, Connecticut). Individual PCR reactions were performed for each marker, as described by PE-ABI using AmpliTag DNA Polymerase. The reactions were added to 3.5 μl of loading buffer containing deionized formamide, blue dextran and TAMRA 350 size standards (PE-ABI). After heating at 95°C for 5 minutes to denature the DNA, the samples were loaded and electrophoresed as described in the operator's manual for the Model 377 DNA Sequencer (PE-ABI, Foster City, California). After gel electrophoresis, the data was analyzed using PE-ABI GENESCAN™ and GENOTYPER™ software. First, within the GENESCAN™ software, the lane tracking was manually optimized prior to the first step of analysis. After the gel lane data was extracted, the standard curve profiles of each lane were examined and verified for linearity and size calling. Lanes, which had problems with either of these parameters, were re-tracked and verified. Once all lanes were tracked and the size standards were correctly identified, the data were imported into GENOTYPER™ for allele identification To expedite allele calling (binning), the program Linkage Designer from the Internet web-site of Dr. Guy Van Camp (http://alt.www.uia.ac.be/u/dnalab/ld.html) was used. This program greatly facilitates the importing of data generated by GENOTYPER™ into the pedigree drawing program Cyrillic (Version 2.0, Cherwell Scientific Publishing Limited, Oxford, Great Britain) and subsequent linkage analysis using the program LINKAGE (Lathrop et al, *Am. J. Hum. Genet.*, 37:482-498 (1985)).

III. Linkage Analysis

Fig. 1 demonstrates the pedigree of the individuals used in the genetic linkage studies for this invention. Specifically, two-point linkage analysis was performed using the MLINK and LINKMAP components of the program LINKAGE (Lathrop et al, *Am. J. Hum. Genet.*, 37:482-498 (1985)). Pedigree/marker data was exported from Cyrillic as a pre-file into the Makeped program and converted into a suitable ped-file for linkage analysis.

The original linkage analysis was performed using three models: (i) an autosomal dominant, fully penetrant model, (ii) an autosomal dominant model with reduced penetrance, and (iii) a quantitative trait model. The HBM locus was mapped to chromosome 11q12-13 by analyzing DNA for linked markers from 22 members of a large, extended kindred. A highly automated technology was used with a panel of 345 fluorescent markers which spanned the 22 autosomes at a spacing interval ranging from 6-22 cM. Only markers from this region of chromosome 11 showed evidence of linkage (LOD score ~3.0). The highest LOD score (5.74) obtained by two-point and multipoint analysis was D11S987 (map position 55 in **Fig. 2**). The 95% confidence interval placed the HBM locus between markers D11S905 and D11S937 (map position 41-71 in **Fig. 2**). Haplotype analysis also places the Zmax1 gene in this same region. Further descriptions of the markers D11S987, D11S905, and D11S937 can be found in Gyapay et al, *Nature Genetics*, Vol. 7, (1994).

In this invention, the inventors report the narrowing of the HBM interval to the region between markers D11S987 and GTC_HBM_Marker_5. These two markers lie between the delimiting markers from the original analysis (D11S11S905 and D11S937) and are approximately 3 cM from one another. The narrowing of the interval was accomplished using genotypic data from the markers D11S4191, D11S1883, D11S1785, D11S4113, D11S4136, D11S4139, (Dib et al, *Nature*, 380:152-154 (1996)), FGF3 (Polymeropolous et al, *Nucl. Acid Res.*, 18:7468 (1990)) (information about the genetic markers can be found at the internet site of the Genome Database, http://gdbwww.gdb.org/), as well as the markers GTC_HBM_Marker_1, GTC_HBM_Marker_2, GTC_HBM_Marker_3, GTC_HBM_Marker_4, GTC_HBM_Marker_5, GTC_HBM_Marker_6, and GTC_HBM_Marker_7.

As shown in **Fig. 1**, haplotype analysis with the above genetic markers identifies recombination events (crossovers) in individuals 9019 and 9020 that significantly refine the interval of chromosome 11 to which the Zmax1 gene is

localized. Individual 9019 is an HBM-affected individual that inherits a portion of chromosome 11 from the maternal chromosome with the HBM gene, and a portion from the chromosome 11 homologue. The portion inherited from the HBM gene-carrying chromosome includes markers D11S935, D11S1313, GTC_HBM_Marker_4, D11S987, D11S1296, GTC_HBM_Marker_6, GTC_HBM_Marker_2, D11S970, GTC_HBM_Marker_3, D11S4113, GTC_HBM_Marker_1, GTC_HBM_Marker_7 and GTC_HBM_Marker_5. The portion from D11S4136 and continuing in the telomeric direction is derived from the non-HBM chromosome. This data places the Zmax1 gene in a location centromeric to the marker GTC_HBM_Marker_5. Individual 9020 is an unaffected individual who also exhibits a critical recombination event. This individual inherits a recombinant paternal chromosome 11 that includes markers D11S935, D11S1313, GTC_HBM_Marker_4, D11S987, D11S1296 and GTC_HBM_Marker_6 from her father's (individual 0115) chromosome 11 homologue that carries the HBM gene, and markers GTC_HBM_Marker_2, D11S970, GTC_HBM_Marker_3, GTC_HBM_Marker_1, GTC_HBM_Marker_7, GTC_HBM_Marker_5, D11S4136, D11S4139, D11S1314, and D11S937 from her father's chromosome 11 that does not carry the HBM gene. Marker D11S4113 is uninformative due to its homozygous nature in individual 0115. This recombination event places the centromeric boundary of the HBM region between markers D11S1296 and D11S987.

Two-point linkage analysis was also used to confirm the location of the Zmax1 gene on chromosome 11. The linkage results for two point linkage analysis under a model of full penetrance are presented in Table 1 below. This table lists the genetic markers in the first column and the recombination fractions across the top of the table. Each cell of the column shows the LOD score for an individual marker tested for linkage to the Zmax1 gene at the recombination fraction shown in the first row. For example, the peak LOD score of 7.66 occurs at marker D11S970, which is within the interval defined by haplotype analysis.

TABLE 1

Marker	0.0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4
D11S935	- infinity	0.39	0.49	0.47	0.41	0.33	0.25	0.17	0.10
D11S1313	- infinity	2.64	2.86	2.80	2.59	2.30	1.93	1.49	1.00
D11S987	- infinity	5.49	5.18	4.70	4.13	3.49	2.79	2.03	1.26
D11S4113	4.35	3.99	3.62	3.24	2.83	2.40	1.94	1.46	0.97
D11S1337	2.29	2.06	1.81	1.55	1.27	0.99	0.70	0.42	0.18
D11S970	7.66	6.99	6.29	5.56	4.79	3.99	3.15	2.30	1.44
D11S4136	6.34	5.79	5.22	4.61	3.98	3.30	2.59	1.85	1.11
D11S4139	6.80	6.28	5.73	5.13	4.50	3.84	3.13	2.38	1.59
FGF3	0.59	3.23	3.15	2.91	2.61	2.25	1.84	1.40	0.92
D11S1314	6.96	6.49	5.94	5.34	4.69	4.01	3.27	2.49	1.67
D11S937	-infinity	4.98	4.86	4.52	4.06	3.51	2.88	2.20	1.47

A single nucleotide polymorphism (SNP) further defines the HBM region. This SNP is termed SNP_Contig033-6 and is located 25 kb centromeric to the genetic marker GTC_HBM_Marker_5. This SNP is telomeric to the genetic marker GTC_HBM_Marker_7. SNP_Contig033-6 is present in HBM-affected individual 0113. However, the HBM-affected individual 9019, who is the son of 0113, does not carry this SNP. Therefore, this indicates that the crossover is centromeric to this SNP. The primer sequence for the genetic markers GTC_HBM_Marker_5 and GTC_HBM_Marker_7 is shown in Table 2 below.

TABLE 2

Marker	Primer (Forward)	Primer (Reverse)
GTC_HBM_ Marker_5	TTTTGGGTACACAATTCAGTCG	AAAACTGTGGGTGCTTCTGG
GTC_HBM_ Marker_7	GTGATTGAGCCAATCCTGAGA	TGAGCCAAATAAACCCCTTCT

The kindred described have several features of great interest, the most important being that their bones, while very dense, have an absolutely normal shape. The outer dimensions of the skeletons of the HBM-affected individuals are normal, and, while medullary cavities are present, there is no interference with hematopoiesis. The HBM-affected members seem to be resistant to fracture, and there are no neurologic symptoms, and no symptoms of impairment of any organ or system function in the members examined. HBM-affected members of the kindred live to advanced age without undue illness or disability. Furthermore, the HBM phenotype matches no other bone disorders such as osteoporosis, osteoporosis pseudoglioma, Engelmann's disease, Ribbing's disease, hyperphosphatasemia, Van Buchem's disease, melorheostosis, osteopetrosis, pycnodysostosis, sclerostenosis, osteopoikilosis, acromegaly, Paget's disease, fibrous dysplasia, tubular stenosis, osteogenesis imperfecta, hypoparathyroidism, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, primary and secondary hyperparathyroidism and associated syndromes, hypercalciuria, medullary carcinoma of the thyroid gland, osteomalacia and other diseases. Clearly, the HBM locus in this family has a very powerful and substantial role in regulating bone density, and its identification is an important step in understanding the pathway(s) that regulate bone density and the pathogenesis of diseases such as osteoporosis.

In addition, older individuals carrying the HBM gene, and therefore expression of the HBM protein, do not show loss of bone mass characteristic of normal individuals. In other words, the HBM gene is a suppressor of osteoporosis. In essence, individuals carrying the HBM gene are dosed with the HBM protein, and, as a result, do not develop osteoporosis. This *in vivo* observation is strong evidence that treatment of normal individuals with the HBM gene or protein, or a fragment thereof, will ameliorate osteoporosis.

IV. Physical Mapping

To provide reagents for the cloning and characterization of the HBM locus, the genetic mapping data described above were used to construct a physical map of

the region containing Zmax1 on chromosome 11q13.3. The physical map consists of an ordered set of molecular landmarks, and a set of BAC clones that contain the Zmax1 gene region from chromosome 11q13.3.

Various publicly available mapping resources were utilized to identify existing STS markers (Olson et al, *Science*, 245:1434-1435 (1989)) in the HBM region. Resources included the GDB, the Whitehead Institute Genome Center, dbSTS and dbEST (NCBI), 11db, the University of Texas Southwestern GESTEC, the Stanford Human Genome Center, and several literature references (Courseaux et al, *Genomics*, 40:13-23 (1997), Courseaux et al, *Genomics*, 37:354-365 (1996), Guru et al, *Genomics*, 42:436-445 (1997), Hosoda et al, *Genes Cells*, 2:345-357 (1997), James et al, *Nat. Genet.*, 8:70-76 (1994), Kitamura et al, *DNA Research*, 4:281-289 (1997), Lemmens et al, *Genomics*, 44:94-100 (1997), Smith et al, *Genome Res.*, 7:835-842 (1997)). Maps were integrated manually to identify markers mapping to the region containing Zmax1.

Primers for existing STSs were obtained from the GDB or literature references are listed in Table 3 below. Thus, Table 3 shows the STS markers used to prepare the physical map of the Zmax1 gene region.

TABLE 3: HBM STS Table

STS Name	Locus Nam	Type	GDB Access.	Size (kb)	Forward Primer	Reverse Primer	Gene Name
ACTN3		Gene	GDB:197568	0.164	CTGGACTACGTGGCCTTCTC	TTCAGAAGCACTTGGCTGG	Actinin, alpha 3 - skeletal muscle
PC-B/PC-Y		Gene	GDB:197884	0.125	CTCAGTGCCATGAAGATGGA	CAAGATCACTCGATCTCCAGG	Pyruvate Carboxylase
	D11S2161	Gene		0.322	GTTTCAGGAGACTCAGAGTC	TTCTGCAGGTTGCTGTTGAG	Adenosine Receptor (A2) Gene
ADRBK1		Gene	GDB:4590178	0.117	TTATTGTGATTTCCCGTGGC	GCCCTCTGTCCTGACTTCAGG	Beta-adrenergic receptor kinase
PSANK3		GENE		0.259	GAGAAAGAAATAAGGGGACC	TGCTTTGTAAAGCACTGAGA	sim. to Human endogenous retrovirus mRNA long terminal repeat
PP1(1/2)/PP1(2/2)		Gene	GDB:197566	0.208	GAAGTACGGGCAGTTCAGTGGCCT	ATACACCAAGGTCCATGTTCCCCGT	Protein phosphatase 1, catalytic subunit, alpha isoform
GSTP1.PCR1		Gene	GDB:270066	0.19	AGCCTGGGCCACAGCGTGAGACTAC	TCCCGGAGCTTGCACACCCGCTTCA	Glutathione S-transferase pi
NDUFV1		Gene		0.521	CATGTGCCCACCTCATTCAT	CAAGATTCTGTAGCTTCTGG	NADH dehydrogenase (ubiquinone) flavoprotein 1 (51kD)
PSANK2		GENE		0.157	CAGAGAAGTCAAGGGACTTG	ATCCTCTCACATCCCACACT	Aldehyde Dehydrogenase 8 (ALDH8)
PSANK1		EST		0.3	CAAGGCTAAAAGACGAAAAA	TCAGGAGCATTTCATCTTTT	Human ribosomal protein L37 (PSANK1) pseudogene.
UT5620	D11S1917	MSAT	GDB:314521	0.211	AAGTCGAGGCTGCAAGGAG	GCCCTGTGTTCCTTTCAGTA	
AFM289ya9	D11S1337	MSAT	GDB:199805	0.287	AAGGTGTGAGGATCACTGG	AGCTCATGGGGGCTATT	
GALN		Gene		0.322	GCTTCTCCGAGTGTATCAAC	ATGGCAGAGGACTTAGAACA	Preprogalanin (GAL1)
pMS51	D11S97	VNTR	GDB:177850		GATCAGCGAACTTCCTCTCGGCTC	TCCACATTGAGGACTGTGGGAACG	
BCL1(1)/BCL1(2)		Gene		0.205	GCTAATCACAGTCTAACCGA	TTGCACTGTCTTGGATGCA	B-cell CLL/lymphoma 1 - Cyclin D1 (PRAD1 gene)
CCND1		Gene	GDB:4590141	0.248	GCACAGCTGTAGTGGGGTTCTAGGC	CAGGCGCAAAGGACATGCACACGGC	Cyclin D1
FGF4		Gene	GDB:4590113	0.649	CACCGATGAGTGCACGTTCAAGGAG	CAGACAGAGATGCTCCACGCCATAC	Fibroblast growth factor 4
FGF3.PCR1		Gene	GDB:188627	0.161	TTTCTGGGTGTGTCTGAAT	ACACAGTTGCTCTAAAGGGT	Fibroblast growth factor 3
AFM164ZF12	D11S913	MSAT	GDB:188161	0.22	CATTTGGGAAATCCAGAAGA	TAGGTGTCTTATTTTTTGTTGCTTC	
AFMA190YD5		MSAT	GDB:1222329	0.275	GACATACGATGAACACTATAAGAGG	CAACCCATACCAGGGATAAG	
SHGC-15285	D11S4689	STS	GDB:740600	0.147	GAACAAGAGGGGTAAGTTGGC	TGAGGACACAGATACTGATGGG	
SHGC-3084	D11S4540	STS	GDB:740102	0.167	GAAGTGTTCCCTCTTAAATTCTTTG	GAACTATATTGTAGTTAGTGAGGAG	
SHGC-14407	D11S4664	STS	GDB:740516	0.158	CCTGTAACCCCCAGTCCC	TCTTGCTTCCTAAGTTTCTCGG	
SHGC-10946	D11S4327	Gene	GDB:674522	0.311	ACTCCATCCACCTCATCACTG	TGCTGTTTGCCTCATCTGAC	Choline Kinase
S515	D11S703	STS	GDB:196290	0.166	GTGGACAGGCATAGCTGAGG	TGTTCACTCTTCTGCCTGCAG	
AFM147XD10	D11S1889	MSAT	GDB:307885	0.183	AGCTGGACTCTCACAGAATG	CAAGAGGCTGGTAGAAGGTG	
AFMA131YE5	D11S987	MSAT	GDB:195002	0.082	GACTCCAGTCTGGGCAATAAAAGC	GGTGGCAGCATGACCTCTAAAG	
AFMb358xa9	D11S4178	MSAT	GDB:611922	0.237	CAGGCCCAGTCTCTTG	CGTGTCCAGATGAAAGTG	
AFMa272yb5	D11S4113	MSAT	GDB:608115	0.218	ACCTCACGGTGTAATCCC	CTTGAAGCCCATCTTTGC	
WI-17803		EST	GDB:4581644	0.15	TATTTGCAAAGCTTGAGACTTCT	AATCACTGTGCTTTGTTGCC	
SGC31923		EST	GDB:4578606	0.126	ACTTTATTGTCAGCGTGGGC	ACTCCCTCGATGGCTTCC	
WI-7741	D11S4384	GENE	GDB:677652	0.324	GAGCAGGGGAGAGAAGGC	CCCAACTGGCTTGTTTTATTG	Transformation-sensitive protein IEF SSP 3521
SGC35223		EST	GDB:4582598	0.13	AGCCACTTTATTGTTATTTTGATGC	AAGAGTGAACAAAAGCAAACATACC	ZNF162 - splicing factor 1
WI-16754		EST	GDB:4578377	0.15	GTGGAGTGTGGGATTGGG	TACTGTTCTTGATAAGTATGTCGGC	
WI-6315	D11S4418	EST	GDB:678804	0.224	ATGCTTTTGCATGATTCTAATTATT	TCCCCCAAAAGAATGTAAAGG	
WI-16915		EST	GDB:4584055	0.125	CTGGTCTTCCTTGTGTGCTG	ATCACCCAGGCCAGGGAT	Mitogen inducible gene (MIG-2)
SGC30608		EST		-0.128	TCAGAAGCAGAACTGTTTTTAACA	CCTGCTTGAAAGTTCTAGAGCC	
WI-17663		EST	GDB:4583346	0.126	CAAGCCGGGTTTTATTGAAA	GATGCCAGGACCATGGAC	
WI-6383		Gene	GDB:1222237	0.199	GCATATAGAAACAATTTATTGCCG	CTCTGAAGCAGGGACCAGAG	Human tat interactive protein (TIP60)
SGC31567		Gene	GDB:4578432	0.207	CTACCACACCACACCAGGC	CAAGCGAAAGCTGCCTTC	Calcium activated neutral protease large subunit, muCANP, calpain
SGC30658		EST	GDB:4584037	0.15	GTTGTCTTGACTTCAGGTCTGTC	TTTTCCTTCAACAATCACTACTCC	
SGC34590		EST		0.13	GCGTGGGGATATAGAGGTCA	TACGTGGCCAAGAAGCTAGG	
SGC33927		EST	GDB:4582382	0.15	TAATATATCCCCAGTCTAAGGCAT	AGCTTGCAGATGGAGCCC	
WI-8871		EST	GDB:1222235	0.124	TGGTTTTAAACCTTTAATGAGAAAA	TGTTGATCTATACCCTGTTTCCG	
WI-12334		EST	GDB:1222257	0.127	AATTATTTAAAAGAGAGGAAAGGCA	TGGCTGTGAACTTCCTCTGA	
WI-18402		EST	GDB:4581874	0.113	GGTTACAGAAAAACATTTGAGAGAT	TGAGCTTTAGTTCCCTTCTCTG	
WI-18571		EST	GDB:4584947	0.131	TTGAAAAACCATTTATTTCACCG	TCTGCGGCTGTTGGATTT	Hlark
WI-12056		EST	GDB:4576606	0.209	TTGAAAAACCATTTATTTCACCG	TGTTCTCTTCTCCCAGCAGG	Hlark
SGC33767		EST	GDB:4581106	0.15	CTTTATTGAAAACATTGAGTGCA	TTGTCAAATTCCCCCCAAAA	
AFM343YB5		MSAT	GDB:1222332	0.181	AAACCACGACCNCCAA	CCCTGGAAAGGTAAGATGCT	
SGC33744		EST	GDB:4575826	0.15	CTTTTGGTAGAGACAAGGTCTCA	TATCTGTCTGTAGTGCTTCAAATGT	
SGC32272		EST	GDB:4581592	0.135	GACGAAGGTGATTCAGGGC	ACTGAAGAACTCTTGTCCT	
SGC34148		EST	GDB:4583084	0.1	CAGATAAAAGAGTCACTATGGCTCA	CACTTCTCCCACTTTGTCCC	
WI-18546		EST	GDB:4574598	0.133	TTATTGATAAGCATTAGTGAACCCC	TGGCAAGTTAGGCACAGTCA	Human 1.1 kb mRNA upregulated in retinoic acid treated HL-60 neutrophilic cells
SGC31103		EST	GDB:4567265	0.1	CTATGCCCAGAGATGAACAGG	TCCACTAAGGGCTATGTCGC	
SGC30028		Gene	GDB:4580505	0.128	GCCAGCTTTATTGAGTAAACTTCC	CACTGGAGACTACAAGTGGTGG	Human pyruvate carboxylase precursor
WI-2875	D11S4407	STS	GDB:678548	0.125	CATCCCAACCATCACTCAGT	GGGGACTAGCTTACAGATTTGA	
SGC36985		Gene	GDB:4577182	0.223	AGACTACATTTTGGAACCAGTGG	TGAAAGGATATTTATAGCCTGGA	LAR-interacting protein 1b
GCT16B07	D11S4270	STS	GDB:628245	0.137	GAAGGTTTTGTCCCTCGATC	TGAGGGTTGGGAAGATCATA	
WI-6504	D11S3974	EST	GDB:588142	0.174	CCTTCATAGCCACACCCG	CAGCTAACTGTTGACATGCCA	
SGC31049		EST	GDB:4580093	0.15	TCTTTACTGTGCTTACAACTTTCCT	CAACAGTGCAGTCGGTATCG	

TABLE 3: HBM STS Table

TIGR-A002J17		EST	GDB:1222193	0.199	AGATCAGCAAGCAGATAG	CATTCCACATGGATAGAC	NDUFV1
WI-5996	D11S2382	EST	GDB:458683	0.1	CATACCTATGAGGTGTGCTACAGG	GCATTTTCTCATCATCCTTGC	amplaxin (EMS1)
WI-16987		EST	GDB:4575848	0.15	TTACAGCCACCAAGGTTTCC	AGGTGTGTGTGCCAGGTTGA	Nuclear mitotic apparatus protein 1, NUMA
SGC31912		EST	GDB:4567868	0.101	CACTGTTATCTCATTAACTGTGAGG	TTTGATTTTGTGTCTCCCAAA	
WI-13500		EST	GDB:4577893	0.15	CCCCACTCCCACTTTTATTT	CCAGTCACCTTTACTAGTCCTTTG	
CHLC.GAAT1B01.P7933	D11S971	MSAT	GDB:684255	0.103	AGGACACAGCCTGCATCTAG	ACCAGGCATTGCACTAAAAG	
SGC35519		Gene	GDB:4577180	0.134	GATGGGTCACACTAACCTGTCA	ACATTTATATTTGGACATGCAACC	LAR-interacting protein 1a mRNA
WI-11974		EST	GDB:1222255	0.108	AGCATCTTTAATGTGTCAGGCA	ATGTGCTGGGCTGGAAAG	Carnitine palmitoyl transferase I
WI-15244		Gene	GDB:4574740	0.108	TCACATTCAAAAATCGGCAA	CTGCCTGTGTGGTGTCGC	Beta-adrenergic receptor kinase 1, ADRB1
WI-17498		EST	GDB:4583336	0.131	TGTTTTATTTCTCAGTACAAAGCCA	GACCTCCTGTGACACCACG	
WI-9159	D11S4381	EST	GDB:678144	0.111	CCACCAAATTATTTATAGTTCTGCG	GTAAGATTCTCCACTGTTGCACC	FGF4
WI-4232		STS	GDB:1222250	0.175	CCTATAATGGGCTGGACCAA	ACTCCTCATGTGAAGTCACCG	
SHGC-4167		EST	GDB:4566789	0.161	CAGTGTGCACGTTTTCATTT	CAGCATCTTCAGCACTTACC	Human DNA helicase gen (SMBP2)
WI-14303		EST	GDB:4576938	0.15	CTGCATTTATTATGAGAATCAACAG	TGCTGCTGCGAGTCAGAGTC	
WI-16597		EST	GDB:4585666	0.13	CAGGGCACTGAGATACACTTACC	AAGGATCAAGCAGGCATTTG	
RC29S1CATTFOR/RC29S1CATT	D11S970	MSAT	GDB:191084	0.15	ACACATCTCTTCTGTGCCCC	TGAACCCTGGAGGCAGAG	
UT979	D11S1296	MSAT	GDB:198525	0.362	CATTCCCCAGTTTGCAGAC	GTGCTGGGATTACAGGTGT	
1281/1282	D11S1959	EST	GDB:335218	0.07	GCAGAGAAGTCCTGTTAGCC	CCATGCTAGAGAAGCACAAC	
D11S468	D11S468	STS		0.098	AGTGTGGGGCAGGACCTCTG	CAGACAGATAGCCCTGGGTTC	
D11S668	D11S668	STS	GDB:179349	0.143	TCCCTCATCCCCTTGTCTGT	AGCCCCCCTGGGGATAATC	
RH16048		Gene	GDB:4572853	0.188	GATGCTTACCTACCACGGC	AGGATTCCTATCTGGGCTATG	Aldehyde dehydrogenase (ALDH8)
IGHMBP2		Gene	GDB:4590087	0.699	TGGCAGACCATGCTCCGCCT	GAGAAGGCCGGGAGGCTCTG	Human DNA helicase gen (SMBP2)
NUMA		Gene	GDB:4590244	0.277	CTCCATCACAACCAGATTTGAGGCT	GGGTGTGAGCTGCTGCTGAAGG	Nuclear mitotic apparatus protein 1, NUMA
KRN1		Gene	GDB:4590232	0.228	AGTGGGAAACCTCAGGTAGCTCCCG	CAGTTTGGCTCAGACATATGGGGGC	High sulphur keratin, KRN
Cda1ff06	D11S2302	EST	GDB:445887	0.091	CATTAAGTAGTGGGGGGACAG	CAAAGCGACAGTGAGTTAGGG	
RH10753		Gene	GDB:4563588	0.194	GGAGTAGACCATGATTACTG	CATGGTCTATTTATTCTCG	protein phosphatase 2A , PP2A
EMS1		Gene	GDB:459016	0.64	CGCCCTGGATCCTCACACTACA	GGGCATCAGGGGATGGGTAGA	Amplaxin
SHGC-11098	DXS9736	Gene	GDB:737674	0.137	GCTCCTATCTGTGTTTTGAATGG	CCGTGGCATAAGATAAGTAAACG	Androgen Receptor
INPPL1		Gene	GDB:4590093	0.382	CTTGGAGCGCTATGAGGAGGGC	ATGGCAACTGACCTTCCGTCCTG	51C protein,inositol polyphosphate phosphatase-like 1
RH18051		EST	GDB:4572859	0.195	TTGGAGTCACAGGGGC	CAGCACTATCCTTGGGG	NOF1
Cda1cc11	D11S2297	EST	GDB:445869	0.1	AACAAAGCTGCTTAGCACCTG	GATGAGGACCAACTGGTGAC	
1249/1250	D11S1957	EST	GDB:335210	0.247	TTTTCCAATAATGTGACTTC	CAATCCCAACCGTAACAGGC	
NDUFV1	D11S2245	EST	GDB:445695		CTTGATCTCGCCCAGGAAC	GCTCGCTGAAGGATGAAGAC	NDUFV1
AFMb032zg5	D11S4136	MSAT	GDB:609548	0.19	GAATCGCTTGAACCCAG	CCAGGTGGTCTTAACGG	
AFMa059xg9	D11S4196	MSAT	GDB:614025	0.2	GAACGTTNTTCATGTAGGCGT	TAATGGTCGCTGTCCC	
Cda17c12	D11S2288	EST	GDB:445842	0.158	AGGGAAAATGGTATGTGGGGAG	GCAGTGTGTGAAGGCAGG	
SHGC-1364	D11S951E	EST	GDB:4562765	0.137	AGTGGACAAAATGAGGAAAACAGG	CCAACACAGTTTGCTCACATGCC	
RH17410		EST	GDB:4571587	0.126	TGACATCTTTGCATTATGGC	AGTTATCCCACCTGATACCG	
RH17414		EST	GDB:4571595	0.121	AGCTCTTGCTTCTCAGTCCA	CAAAAGTTGTTTCTGTGTTTGTTC	
RH17770		EST	GDB:4572301	0.267	GCCTCTCAAAGTAGTTGGAACC	TGTGTATCCATAGTGCAAAACAG	
SEA		EST	GDB:4590169	0.13	CTCAAGGCCAGGCATCACT	GGACTCTTCCATGCCAGTG	S13 avian erythroblastosis oncogene homolog
RH10689		EST	GDB:4563460	0.107	AATGATGATCTCAACTCTG	ACTGAAGAACTCTTGTCCT	
TIGR-A006P20		EST	GDB:4587692	0.236	GACATCTGTTAGTCTCATAATTC	GGTAACAGTGTCTTGCTT	
TIGR-A007D15		Gene	GDB:4588398	0.24	CTATGTACAAAACAGGAAGAG	ATCCTAGTTTCCTCTCCTT	Menin gene (MEN1)
TIGR-A008B14		EST	GDB:4588882	0.141	GTAAATGAGAAACAGACAAATGA	CTATTGGATGTGATATGTTATGG	
TIGR-A008K11		EST	GDB:4589094	0.203	AAGTAGAAACAAAATGAGGGAC	CCTACCCCAAGGTAACAG	
TIGR-A008P15		EST	GDB:4589662	0.182	ACTTCCTATAAATGGAGGTGAG	GAGGAGCTTCAAGAGGAA	
TIGR-A008T11		EST	GDB:4589278	0.138	CATACTCCTAGACTCAAGGAATC	GAATGATGTACATGAATTCTTTG	
TIGR-A008U48		EST	GDB:4589364	0.107	GTGTTGAGGAGAAAAGCACT	CTCCCAGTAGTCACATTCC	
TIGR-A008X45		EST	GDB:4589838	0.242	CAAGTTACAAATAACTTAAGCCG	CAAGACCCTATCTCTACAAAAAC	
SHGC-11839	D11S4811	Gene	GDB:740339	0.151	TTTATTAGAAGTGACTCTTGGCCC	GACTACCTGCCCTCAGCTTG	Folate receptor 2 (FBP2)
NIB1242	D11S4929	EST	GDB:3888276	0.149	TTCTCATGTACAAAGCGGTC	CCACTGGCTTCTCTCTTTTT	cGMP-stimulated 3',5'-cyclic nucleotide phosphodiesterase PDE2A3 (PDE2A)
SHGC-13599	D22S1553	Gene	GDB:737558	0.147	CACCAGAAGGTTGGGGTG	ACTATTACGACATGAACGCGG	Macrophage Migration Inhibitory factor
SHGC-11867	D11S4331	Gene	GDB:674684	0.14	CTCATGCTGGATGACCCC	TTGCCTTTCTTGAAACTTAATTCC	P2U Purinoceptor
SHGC-15349	D12S2124	EST	GDB:740819	0.141	TCACAGCCTTCAGTCAGGG	ACATGCTGTGGCACCATG	
Bda84a05	D11S2235	EST	GDB:445662	0.095	CCTGAGCTACTGCCACAG	CCCTGACTTGGACAGTGTCC	
Bda99d07	D11S2238	EST	GDB:445874	0.09	TCAGAGTCACTCCTGCCC	CAAATTCAAGCTCATCCAGACC	
folr1		Gene	GDB:197840	0.3	CGGCATTTCATCCAGGAC	GGTGTAGGAGGTGCGACAAT	Folate receptor2 (FBP2)
NIB1738	D11S4284	EST	GDB:626260	0.173	TTCCATTTATTGAGCACCTG	CTTAAGCCACTGTGTTTTGG	
WI-7351	D11S4433	Gene	GDB:679143	0.324	CCTCCTACACCTGCAAAAGC	TGGAAGAACCCCAGAGGAC	Folate receptor3 (FBP3)
WI-14325		EST	GDB:4578507	0.132	AAAGCACAAAAGTAACAGCAACA	GTGTGTGGGCCACAATATTG	
WI-15192		EST	GDB:4575806	0.16	AGAGCACCTTTCCTCAGCAC	AGAATCTCATCACAGGGGCG	

TABLE 3: HBM STS Table

WI-17872		EST	GDB:4577492	0.141	AAAAAGGACAGTGTCTAAAATTTGA	AATTGTTTTTGTTTGTTTTTTGAGT	
SHGC-30732		EST	GDB:4567830	0.105	GATTTAGGGAGTACAAGTGCGG	GGGGACAAATTATACTTTATTCAGG	
stSG4288		EST	GDB:4566057	0.123	CCATCATCATATTGGTGTGACC	TGGCTGCCCAAGAAGAAG	
WI-13814		EST	GDB:4579290	0.15	TTAAGATGCCATTAAACTCATGAC	CCAAGGAGATGACCAAGTGG	(DRES9
WI-14122		Gene	GDB:4576114	0.126	CCATCTCTTTTATCAGGGTTGG	CTCTGTGCAAGTAAGCATCTTACA	Human VEGF related factor isoform VRF186 precursor (VRF)
2729/2730	D11S4057	EST	GDB:596509	0.118	CGACTGTGTATTTTCCACAG	AGAAGCCCATATCAATGCAC	
SHGC-31329		EST	GDB:4567386	0.15	AGCTTAAAGTAGGACAACCATGG	GGATGCTTCACTCCAGAAAG	
SGC33858		EST	GDB:4578600	0.127	TGTTGTTTATTTCCACCTGCC	AGAGTGGCTGCAGGCCAG	
WI-12191		EST	GDB:1222208	0.15	TTTTTTTTTTTACACGAATTTGAGG	TGAGGAAGTAAAAACAGGTCATC	
WI-13701		EST	GDB:4574892	0.15	ATGAAATCTTAAGCAGAATCCCA	CACAGAGTCCCAGGGTCTGT	
WI-14069		EST	GDB:4584373	0.15	AAAGGCCTTTATTTATCTCTCTCTG	GCCTCAGAGCTGGTGGGT	
WI-14272		EST	GDB:4578525	0.125	GCTTCTAAGTCTTAGAGTCAGCTGG	AGCCCACAGTCAGCCTACC	
WI-17347		EST	GDB:4578523	0.127	TTGGTTAAATGATGCCCAGA	TGGTCCCACTCACATCCC	
stSG1581		EST	GDB:4564416	0.215	ACACAGCATGCAGGGAGAG	ATCCCTGGTGCTTAGGTGG	
stSG1938		EST	GDB:4564568	0.137	GATGGAAGTAGCTCCTCTCGG	GGAAGGCCAGCAAGTACTACC	
stSG2769		EST	GDB:4565137	0.141	CCGGTGCTTGGAAAGATG	GAAGTGTCTCTGTTGGGGGA	
RH97		EST	GDB:4559690	0.17	TTACAGGCATGAGTCACTACGC	ACCACTCTCACAGCCCTTACA	
stSG4794		EST	GDB:4573113	0.141	CCCTCCCTCCACACACAC	GCTCACTGAACTTTCAGGGC	
stSG4957		EST	GDB:4569051	0.171	AGATACGGGCAAAACACTGG	GTTGAATATAGAGCAGGGCCC	
stSG4974		EST	GDB:4569063	0.166	TTCTGAGGTCAGGGCTGTCT	AGCTTGGAAAATCTCGTGTCA	
stSG8144		EST	GDB:4573137	0.17	ACTCAGTCCCTCCCACCC	TCCTCTCACTCCTTCCCAGA	
stSG9275		EST	GDB:4569999	0.19	GTGATCACGGCTCAACCTG	TGGAGGACTGCTTGAGCC	
SHGC-10667	D11S4583	Gene	GDB:740246	0.277	CTGCAGCTGCCTCAGTTTC	TCAAAAGTGCTGGTGACAGC	Human protein kinase (MLK-3)
SHGC-11930		Gene	GDB:1231223	0.21	ATTTCCAGAGCCAGCTCAAA	CTTTAATGTTGTGATGACACAAAGC	FGF3
SHGC-32786		EST	GDB:4567876	0.125	GATCATGCACTGTTGACCAC	TACATTTGAAACATTTAAAACCTGA	
FKBP2		Gene		0.064	AACTGAGCTGTAACCAGACTGGGA	TGGAACAGTCTGGTCCTGATGG	FK506-Binding Protein Precursor (FKBP-13)
WI-13116		EST	GDB:4585099	0.202	TTATCCCTTTATTGTTTCTCCTTTG	TGGTCACCTGTATTTATTGCTAGG	
MDU1		Gene	GDB:4590064	0.859	TCTTCAAAGCCTCTGCAGTACC	CTCATCTCCAACCTGTCTAACC	4F2 Cell.-Surface Antigen Heavy Chain (4F2HC)
S453	D11S579	STS	GDB:196276	0.108	GTGGCTGCAGCTAATGTAAGACAC	CAGCAGAGACAATGGCGTAAGTCC	
STS1-cSRL-112e11	D11S3866	STS	GDB:547681	0.135	CTGATTGAGAACCAGAACAG	TAAAGCCCTATAACCTCTCC	
STS1-cSRL-44a3	D11S3830	STS	GTC:547609	0.118	TAGTAAGGGACCTTCACCAG	AGATGTTTGGTATGACTTGG	
STS1-cSRL-31b12	D11S2439	STS	GDB:459728	0.123	GATGATTAAACTCTCCTGGC	GAGACAGCTAAGCACTCATG	
cSRL-4I9	D11S1137	STS	GDB:197824	0.196	GAGGTGGTGGGCACCTGTA	AGAGGGGAGGAACACACCTT	Folate receptor2 (FBP2)
SHGC-10323	D11S4351	Gene	GDB:676135	0.141	GACCAGAGTCTGCCCAGAAG	TCCCCAGCTCTATCCCAAC	Collagen binding protein 2, colligin-2 gene (CBP2)
WI-9219		Gene	GDB:676179	0.1	GGAGGGATGGACAAGTCTGA	GTCCAGCTCGCTGACTATCC	Retinal outer segment membrane protein 1, ROM1
GTC_ZNF		Gene		0.172	TCAAAACACAGTCATCTCCA	GCAAAGGCTTTACCATATTG	ZNF126
AFMa152yh1	D11S4087	MSAT	GDB:603787	0.158	GCTCAGCACCCCCATT	TCCCTGCTCGGGAAAC	
AFMb331zh5	D11S4162	MSAT	GDB:611241	0.263	GTTCTCCAGAGAGACAGCAC	GAGAGCAACACTATTGCCC	
AFMb038yb9	D11S4139	MSAT	GDB:609621	0.151	TATAGACTTCAGCCCTGCTGC	CCTCTGTAGGATGCAGTTGG	
AFM212xe3	D11S1314	MSAT	GDB:199292	0.209	TTGCTACGCACTCCTCTACT	GTGAAGGCAGGAAATGTGAC	
WI-18813		EST		0.13	ATCCTAGACCAGAGGAGCCC	CTCCCCCTGGTCCAGTTATT	Serine/threonine kinase
WI-19549		EST		0.252	AACTTTCATTTGCCAAGGGA	AGCAGATCTGCTCTTGCGAT	
WI-20154		EST		0.25	ACAGTTGTCATCGGTAGGCA	AAAAGTATGAATGGGATGGAGC	
WI-22393		EST	GDB:4583084	0.142	GTGCAGGTGGCGTTTATTTT	CCCTATATCTCCGTGTGCTCC	DRES9
WI-7587		EST	GDB:1223732	0.274	GCTCTAGTGGGAAACCTCAGG	GAATTCCAGGCTCTTGCTTG	Ultra high-sulphur keratin protein (KRN1)
EST455578		EST		0.273	GGTTTGGTCTCAAAGGCAAA	CCAGTACATGGTGGTCACCA	
WI-21134		EST		0.293	GCTGCCTTGGAATTTCTGTT	GTGCTGTGGTGGGGAAAG	Fas-associating death domain-containing protein, FADD
WI-21698		EST		0.25	ATTCAAGCTCATCCAGACCC	GGACTGGCCCTTTGAAACTC	
SHGC-7373	D11S4567	STS	GDB:740192	0.225	ATATTGACCGTGCACAAATACG	AGACCTGGGAAAAGTGGAGAA	
SHGC-38533		STS		0.125	ATTGGCAGTGGAAAATGCTT	TTAATCTTTTGTCAACTTCCTGATT	
ARIX		Gene		0.242	tctgtcctccttcaccggaagc	ggataaagaaactccgctctgctggtaga	Arix homeodomain protein, neuroendocrine specific, tx factor
CLCI,PCR		Gene	GDB:6262613		TCAGGGCCTGTGTTGCCGCACTCTG	AGCGATGTAAAGGGTACCAGTGCCG	Chloride channel current inducer, ICLN gene
B188N21-HL		STS			AGGCATGCAAGCTTCTTA	CCGGGAGGAGACATCTAT	
B234C17-HR		STS			TGGTAAGCACAGAAAATGC	AATGGATGGGGGATTATT	
B235G10-HR		STS			CTGGACGTTATGTCTGCC	AGAGGCCCAGTCACAGAT	
B247F23-HR		STS			ATCACTCTGAACTGCCACT	CCCTTCTGTTTTTCTGTTTT	
B337H24-HL		STS			CAAGCTTTGAAGGAAGAG	TAGGACGTTAAGTGAGGAC	
B337L5-HL		STS			GCTCTGCAGTGGGTAAAA	ACTCTCCAAGACTGTGCG	
B382N10-HR		STS			CCCTTTCTGAGGCAAGAT	GACCACCTGGGAGAGAAC	
B12I1-HR		STS			CGCTATGAGTCCCATCTG	GATCAGCTGCAATGAAGG	
B180D17-HR		STS			TTGAGTACACGGGGTGAC	CGCAGGACTGAAAGATGA	
B236E6-HR		STS			ACCTGTCTCCTCTCCTGG	TGCTTTTCTTCTGTGGGA	

TABLE 3: HBM STS Table

B278E22-HR		STS			ATGACCAGCAAGCATTGT	GTACTGGGATTACAGGCG	
B312F21-HR		STS			GCAGAAGGTCCTTTGGAT	TTTGCAGGATTCATGCTT	
B337H24-HR		STS			CGACATTCTTTTCTGGAGG	ACCTTTGCATGTTGGTTTT	
B358H9-HR		STS			GCACTTTTCCTTCCTTCC	TGCTTTGCTTTCTTCTGG	
B148N18-HL		STS			ACAGCTCCAGAGAGAAGGA	GCAGTCACTTGAAACCAGA	
B172N12-HL		STS			AGGCATCAAGCTTTCCTT	GGTTTAGAGAACCGAGCC	
B172N12-HR		STS			GTGGTGCTGCAAGTTACC	GGAATCCCTTTCTTTCCA	
B215J11-HR		STS			GACCATTTGTTACGCAGC	GATGGGTGTGAATGAACAA	
B223E6-HR		STS			CTCAAGCTTCTGTTCATGC	GCTGTGAGTGTCTTGGCT	
B312B3-HR		STS			TACAGAAAACCGCAGCTC	GCCACCAAAGGAAAGATT	
B328G19-HL		STS			AAAAGGAGGGAATCATGG	TCACTTAGCAGGAGGCAG	
B328G19-HR		STS			CTGAGCATCCGATGAGAC	GTGCAAAATGAGCAGCTT	
B329I10-HL		STS			TCTAACCCCTTACTGGGC	TCCTCAAACTGGGAATGA	
B329I10-HR		STS			TTTACACAGGACCAGGGA	ATCTCCCCCACTCAGAAG	
B368G19-HL		STS			GTCCACGGGCTTTATTCT	TGAGCATAAATTTCATTAGCTG	
B368G19-HR		STS			GGAAGAGCAAAATAAATCCA	GGTGCACAGAATTGTTCAT	
B36F16-HL		STS			AGCACGCTTATTTCATGG	GTAACACCAGCAGGGACA	
B250K11-HR		STS			TCCTGCTGCATTATGGAT	GGGGGTGAGAAGTAGGAA	
B338D17-HR		STS			ATGGGGATTAAATACGGG	AGCTAGCATTGGGCTCTT	
B288I23-HL		STS			CTGAGGAGAAGAGGCTGG	CGCCTTACAAGGCAAGTA	
B288I23-HR		STS			AGGATGCTTGCTAGGGTT	CACAAGTGTCTGGAAGGC	
B371E15-HR		STS			GGTCTCAGGAGCCCTTTA	ACATGCCACTCTTCTCACTAA	
B312F21-HL		STS			ACTTAACCAAGGATGGGG	CAACCCACGAGCATAAGA	
B338D17-HL		STS			TAGGCTCTGCACTCTTGG	ACCCACGGAGTCTCTCTC	
B369H19-HL		STS			TAAAGGCGGTGAAGTGAG	CTACCGCTCTCCTAGGCT	
B369H19-HR		STS			TGGGGCCAGATAATTCTT	CTGGTGTTTGGTGGTGTT	
B444M11-HR		STS			AAGGAAGAGGTCACCAGG	CACAAATTCCATTTCCCA	
B269L23-HL		STS			TCAATAGGTGATCCAACATTT	AAAGTCCCACAAAGGGTC	
B250K11-HL		STS			GGGTAGGGGGATCTTTTT	TGTGGAACATTCATTGGC	
B269L23-HR		STS			GTCCTGGGAAAGATGGAA	TCAAAGCGTCTCCCATAA	
B364H4-HL		STS			TCTTTCGCTGTACTTGGC	TGGGAGGTCAGAGTGATG	
B364H4-HR		STS			GGACAGTGTATGTGTTGGG	AGGCAGCTGTTTTTGTGA	
B473O3-HR		STS			CTTCTTGAGTCCCGTGTG	CAACCGAGAATCCTCTAGC	
B180D17-HL		STS			GCTGGGAGAGAATCACAA	GCTTTGCAGAAGAGACCA	
B200E21-HL		STS			ACGCTGTCAGGTCACACT	GGAGGATGCTCAGGTGAT	
B200E21-HR		STS			TAGGGGGATCTTTTTCCA	GAGCAATTTGAAAAGCCA	
B14L15-HR		STS			ATGGTCCAGCTCCTCTGT	ATAGAGCACCCCATCTCC	
B442P6-HR		STS			AACATTGCTGTTAGCCCA	GCAATCGAAACAGCATTC	
B188N21-HR		STS			ATGAGTTGGCAGCTGAAG	AATGAAGGTCTTGCCTCC	
GTC-ARRB1		Gene		0.067	GAGGAGAAGATCCACAAGCG	TCTCTGGGGCATACTGAACC	Beta-arrestin-1
B508A5-HL		STS			CTGAGCTTTTGGCACTGT	CTGCTAGGTGACAGCAGG	
B36F16-HR		STS			TGTATGAGTCTGGAGGGTGT	ACACCTGGCTGAGGAAAT	
B117N18-HL		STS			GCAGGGGACGTGATAATA	TTTTGCTTCCTACCATGC	
B14L15-HL		STS			AAAATTGTGAGCACCTCC	TTTATATTTAAAGTGGCTTTGTT	
B21K22-HL		STS			GTGCAAAGCCCACAGTAT	AGGAAAATGCAAGAGCAG	
B21K22-HR		STS			CCACTGAATTGCATACTTTG	TCTGGGTCCAGTCTGCTA	
B223E5-HL		STS			AGATTTTGGGGAGTCAGG	GCGCTCAAGCAATTCTC	
B278E22-HL		STS			CAAGCCCCAAAGTAGTCA	GAATCATCCAATCCACGA	
B444M11-HL		STS			AGCCTCCAGGTGACTACC	GAAGGACATGGTCAGCAG	
B543O19-HR		STS			ATGCTTTCAGCATTTTCG	TGATCCGTGGTAGGGTTA	
B117N18-HR		STS			GTCGGATTGGTTTCACAA	TTTTATGGGAATTTCAGCC	
B543O19-HL		STS			TTTGGAAAAGAACAGAAATGT	GGCTAGTCTTTCCTGAACC	
B442P6-HL		STS			CCTTAATGCCCCTGATTC	GCGTTTACAAGCTGAGGA	
B367H4-HR		STS			TCAAGCTTGCTTTCTCAA	GTAGCCCAGCAAGTGTCT	
B250E21-HR		STS			CCTGGCTGGAGATAGGAT	CTTCCCCTCTGCCTATGT	
B250E21-HL		STS			GGCACGTACTTCCTACCA	GGTGCTTCTTACAGGCAA	
B248C16-HR		STS			ACCCAGGCTGGTGTGT	ACTGAGTTAATTATCACTCCCCT	
B248C16-HL		STS			GATGCATTTTGCTTCACC	TCTGCTTTTAGAGCTGTTAGC	
B160D8-HR		STS			TCAAGCTTCAAAGAGCAGA	GGAGTACATCCCAGGACC	
B539L7-HR		STS			TGGTGCTTTTAAATCCAGA	CTCCCTTACTTACTTGCATTG	
B473O3-HL		STS			TCTTCTCCCAGGGAATCT	TTTATGTCCCCTGAGCAC	
AFMa190xd9	D11S4095	STS	GDB:606064	0.193	TCCCTGGCTATCTTGAATC	CTTGACTGGGTCCACG	

TABLE 3: HBM STS Table

ARRB1(2)		STS			CGAGACGCCAGTAGATACCA	CATCCTCCATGCCTTTCAGT	
ARRB1(1)		STS			AGTTCCAGAGAACGAGACGC	CTTGTCATCCTCCATGCCTT	
P102F3S		STS	GDB:6054145		GAGCGTGAGAGGTTGAGGAG	AAACAAACTCCAGACGCACC	
N172A		STS	GDB:6054146	0.208	CTGAACCACTACCTGTATGACCTG	CTAACTACTTACTCCTACAGGGCCC	
N60A		STS	GDB:6054147	0.23	GAAGCATTTCAATACTTTAACTG	CCACTCCAGTGCACCCAATC	
cCI11-44A		STS	GDB:6054148	0.239	CTTCTCCTGGCCACTCTGAC	GGTTTACCTTTGAATCCCAGC	
CN1677-2A		STS	GDB:6054149	0.271	TGAGGATGAATGAGCACATAGG	TTTGTGGTCCATTGAGTAGGC	
cCI11-524B		STS	GDB:6054150	0.221	AGGGGAAGGAATGTGCTTGG	TTCGGCTGAGCGGGCAGTGT	
P117F3T		STS	GDB:6054151	0.188	ATTGAAGGTCCTCCAAAAGAATGCTG	AGAACGTCAACATATCTTTTTGGGGGACAC	
ARRB1(3)		Gene			TTGTATTTGAGGACTTTGCTCG	CGGTACCATCCTCCTCTTCC	
B215J11-HL		STS		0.122	TTTTTGCCTCATCTATGCCC	GGGTGACAGAGCAAGACTCC	
B317G1-HR		STS			TTGCTCAAGTTCTCCTGG	ACCTTGTTTTGAGGGGAG	
B317G1-HL		STS			CTTGGCTATTTGGACAGC	GGGCATTTACTCACTTGC	
B292J18-HR		STS			CTTGTGTCAGTTGTCAGGG	TGGAATTGTTGTGTCTTGG	
B10A18-HL		STS			CCAGTTCCACTGGATGTT	ATGGGCTGTGTTTCTCAA	
B10A18-HR		STS			CTGCCTATCCCTGGACTT	AGTTTGTCCCTAGTGCCC	
B527D12-HL		STS			CAACACGTCTGACATCCAT	GGATAGTGCACACCCA	
B372J11-HR		STS			TGGGTGGTACTATTGTTCCCAT	AGTTCCAGCCCCCTTACCAG	
B372J11-HL		STS			GGCCACTATCATCCCTGTGT	TTTCACATGGGAAGAACACG	
B37E17-HR(GS)		STS			ACAGTGACACTAGGGACGGG	TGCCAGGATGGAGATAACAA	
B37E17-HL(GS)		STS			CCTGTGGCACACATATCACC	ACAACCAAGAATGGAGCCAC	
B34F22-HR(GS)		STS			TGCTGTGTAACAAGTCCCCA	TGAACGGAGGACCTACCAAG	
B34F22-HL(GS)		STS			GCAGGGTCCGACTCACTAAG	GCTGTGAGTTCCCTTTACGC	
B648P22-HR1		STS			ACAGTGGGGACAAAGACAGG	TACAGGGCACCTCCCAGTAG	
B82A4-HR2		STS			TCTTCTGTTAAGGTTTCCCCC	TGTCTCAAACCTCCCTCTGC	
B648P22-HL		STS			AACATATTTCCTCCCCAGCC	CAGTCCCAGCCAATGAGAAC	
B82L11-HL (GS)		STS			CTCCTCTGCATGGGAGAATC	AGACCTGGGACCAGTCTGTG	
B86J13-HL (GS)		STS			GGGAGACGACGTCACAAGAT	TGATGTTGGGAAGATGGTGA	
144A24-HL		STS			CAGGCATCTTCTATGTGCCA	GGGAGGCACAAGTTCTTTCA	
B82L11-HR (GS)		STS			ACTTCGTGGCACTGAGTGTG	CCTTTCTTACGGATGAGGCA	
B86J13-HR (GS)		STS			GGCTGCTGAGCTCTTCTGAT	TGGGTCTCTCTGCCTGACTT	
B82L11-HL2(GS)		STS			TCACCTACTTCCAGCTTCCG	AGACCTGGGACCAGTCTGTG	
B82L11-HL3(GS)		STS			CTCCTCTGCATGGGAGAATC	AATTCAGGAGACCTGGGACC	

Novel STSs were developed either from publicly available genomic sequence or from sequence-derived BAC insert ends. Primers were chosen using a script which automatically performs vector and repetitive sequence masking using Cross_match (P. Green, U. of Washington) and subsequent primer picking using Primer3 (Rozen, Skaletsky (1996, 1997). Primer3 is available at www.genome.wi.mit. edu/genome_software/other/primer3.html.

Polymerase chain reaction (PCR) conditions for each primer pair were initially optimized with respect to $MgCl_2$ concentration. The standard buffer was 10 mM Tris-HCl (pH 8.3), 50 mM KCl, $MgCl_2$, 0.2 mM each dNTP, 0.2 μM each primer, 2.7 ng/μl human DNA, 0.25 units of AmpliTaq (Perkin Elmer) and $MgCl_2$ concentrations of 1.0 mM, 1.5 mM, 2.0 mM or 2.4 mM. Cycling conditions included an initial denaturation at 94°C for 2 minutes followed by 40 cycles at 94°C for 15 seconds, 55°C for 25 seconds, and 72°C for 25 seconds followed by a final extension at 72°C for 3 minutes. Depending on the results from the initial round of optimization the conditions were further optimized if necessary. Variables included increasing the annealing temperature to 58°C or 60°C, increasing the cycle number to 42 and the annealing and extension times to 30 seconds, and using AmpliTaqGold (Perkin Elmer).

BAC clones (Kim et al, *Genomics*, 32:213-218 (1996), Shizuya et al, *Proc. Natl. Acad. Sci. USA*, 89:8794-8797 (1992)) containing STS markers of interest were obtained by PCR-based screening of DNA pools from a total human BAC library purchased from Research Genetics. DNA pools derived from library plates 1-596 were used corresponding to nine genomic equivalents of human DNA. The initial screening process involved PCR reactions of individual markers against superpools, i.e., a mixture of DNA derived from all BAC clones from eight 384-well library plates. For each positive superpool, plate (8), row (16) and column (24) pools were screened to identify a unique library address. PCR products were electrophoresed in 2% agarose gels (Sigma) containing 0.5 μg/ml ethidium bromide in 1X TBE at 150 volts for 45 min. The electrophoresis units used were the Model A3-1 systems from Owl Scientific Products. Typically, gels contained 10 tiers of lanes with 50 wells/tier. Molecular weight markers (100 bp ladder, Life Technologies, Bethesda, MD) were loaded at both ends of the gel. Images of the

gels were captured with a Kodak DC40 CCD camera and processed with Kodak 1D software. The gel data were exported as tab delimited text files; names of the files included information about the library screened, the gel image files and the marker screened. These data were automatically imported using a customized Perl script into Filemaker™ PRO (Claris Corp.) databases for data storage and analysis. In cases where incomplete or ambiguous clone address information was obtained, additional experiments were performed to recover a unique, complete library address.

Recovery of clonal BAC cultures from the library involved streaking out a sample from the library well onto LB agar (Maniatis et al, *Molecular Cloning: A Laboratory Manual.*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1982)) containing 12.5 μg/ml chloramphenicol (Sigma). Two individual colonies and a portion of the initial streak quadrant were tested with appropriate STS markers by colony PCR for verification. Positive clones were stored in LB broth containing 12.5 μg/ml chloramphenicol and 15% glycerol at -70°C.

Several different types of DNA preparation methods were used for isolation of BAC DNA. The manual alkaline lysis miniprep protocol listed below (Maniatis et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1982)) was successfully used for most applications, i.e., restriction mapping, CHEF gel analysis, FISH mapping, but was not successfully reproducible in endsequencing. The Autogen and Qiagen protocols were used specifically for BAC DNA preparation for endsequencing purposes.

Bacteria were grown in 15 ml Terrific Broth containing 12.5 μg/ml chloramphenicol in a 50 ml conical tube at 37°C for 20 hrs with shaking at 300 rpm. The cultures were centrifuged in a Sorvall RT 6000 D at 3000 rpm (~1800 g) at 4°C for 15 min. The supernatant was then aspirated as completely as possible. In some cases cell pellets were frozen at -20°C at this step for up to 2 weeks. The pellet was then vortexed to homogenize the cells and minimize clumping. 250 μl of P1 solution (50 mM glucose, 15 mM Tris-HCl, pH 8, 10 mM EDTA, and 100 μg/ml RNase A) was added and the mixture pipetted up and down to mix. The mixture was then transferred to a 2 ml Eppendorf tube. 350 μl of P2 solution (0.2 N NaOH, 1% SDS) was then added, the mixture mixed gently and incubated for 5 min. at

room temperature. 350 μl of P3 solution (3 M KOAc, pH 5.5) was added and the mixture mixed gently until a white precipitate formed. The solution was incubated on ice for 5 min. and then centrifuged at 4°C in a microfuge for 10 min. The supernatant was transferred carefully (avoiding the white precipitate) to a fresh 2 ml Eppendorf tube, and 0.9 ml of isopropanol was added, the solution mixed and left on ice for 5 min. The samples were centrifuged for 10 min., and the supernatant removed carefully. Pellets were washed in 70% ethanol and air dried for 5 min. Pellets were resuspended in 200 μl of TE8 (10 mM Tris-HCl, pH 8.0, 1.0 mM EDTA), and RNase A (Boehringer Mannheim) added to 100 μg/ml. Samples were incubated at 37°C for 30 min., then precipitated by addition of $C_2H_3O_2Na{\cdot}3H_2O$ to 0.5 M and 2 volumes of ethanol. Samples were centrifuged for 10 min., and the pellets washed with 70% ethanol followed by air drying and dissolving in 50 μl TE8. Typical yields for this DNA prep were 3-5 μg/15 ml bacterial culture. Ten to 15 μl were used for HindIII restriction analysis; 5 μl was used for NotI digestion and clone insert sizing by CHEF gel electrophoresis.

BACs were inoculated into 15 ml of 2X LB Broth containing 12.5 μg/ml chloramphenicol in a 50 ml conical tube. 4 tubes were inoculated for each clone. Cultures were grown overnight (~16 hr) at 37°C with vigorous shaking (>300 rpm). Standard conditions for BAC DNA isolation were followed as recommended by the Autogen 740 manufacturer. 3 ml samples of culture were placed into Autogen tubes for a total of 60 ml or 20 tubes per clone. Samples were dissolved finally in 100 μl TE8 with 15 seconds of shaking as part of the Autogen protocol. After the Autogen protocol was finished DNA solutions were transferred from each individual tube and pooled into a 2 ml Eppendorf tube. Tubes with large amounts of debris (carry over from the pelleting debris step) were avoided. The tubes were then rinsed with 0.5 ml of TE8 successively and this solution added to the pooled material. DNA solutions were stored at 4°C; clumping tended to occur upon freezing at -20°C. This DNA was either used directly for restriction mapping, CHEF gel analysis or FISH mapping or was further purified as described below for use in endsequencing reactions.

The volume of DNA solutions was adjusted to 2 ml with TE8, samples were then mixed gently and heated at 65°C for 10 min. The DNA solutions were then

centrifuged at 4°C for 5 min. and the supernatants transferred to a 15 ml conical tube. The NaCl concentration was then adjusted to 0.75 M (~0.3 ml of 5 M NaCl to the 2 ml sample). The total volume was then adjusted to 6 ml with Qiagen column equilibration buffer (Buffer QBT). The supernatant containing the DNA was then applied to the column and allowed to enter by gravity flow. Columns were washed twice with 10 ml of Qiagen Buffer QC. Bound DNA was then eluted with four separate 1 ml aliquots of Buffer QF kept at 65°C. DNA was precipitated with 0.7 volumes of isopropanol (~2.8 ml). Each sample was then transferred to 4 individual 2.2 ml Eppendorf tubes and incubated at room temperature for 2 hr or overnight. Samples were centrifuged in a microfuge for 10 min. at 4°C. The supernatant was removed carefully and 1 ml of 70% ethanol was added. Samples were centrifuged again and because the DNA pellets were often loose at this stage, the supernatant removed carefully. Samples were centrifuged again to concentrate remaining liquid which was removed with a micropipet tip. DNA pellets were then dried in a desiccator for 10 min. 20 μl of sterile distilled and deionized H_2O was added to each tube which was then placed at 4°C overnight. The four 20 μl samples for each clone were pooled and the tubes rinsed with another 20 μl of sterile distilled and deionized H_2O for a final volume of 100 μl. Samples were then heated at 65°C for 5 min. and then mixed gently. Typical yields were 2-5 μg/60 ml culture as assessed by NotI digestion and comparison with uncut lambda DNA.

3 ml of LB Broth containing 12.5 μg/ml of chloramphenicol was dispensed into autoclaved Autogen tubes. A single tube was used for each clone. For inoculation, glycerol stocks were removed from -70°C storage and placed on dry ice. A small portion of the glycerol stock was removed from the original tube with a sterile toothpick and transferred into the Autogen tube; the toothpick was left in the Autogen tube for at least two minutes before discarding. After inoculation the tubes were covered with tape making sure the seal was tight. When all samples were inoculated, the tube units were transferred into an Autogen rack holder and placed into a rotary shaker at 37°C for 16-17 hours at 250 rpm. Following growth, standard conditions for BAC DNA preparation, as defined by the manufacturer, were used to program the Autogen. Samples were not dissolved in TE8 as part of the program and DNA pellets were left dry. When the program was complete, the

tubes were removed from the output tray and 30 μl of sterile distilled and deionized H_2O was added directly to the bottom of the tube. The tubes were then gently shaken for 2-5 seconds and then covered with parafilm and incubated at room temperature for 1-3 hours. DNA samples were then transferred to an Eppendorf tube and used either directly for sequencing or stored at 4°C for later use.

V. BAC Clone Characterization for Physical Mapping

DNA samples prepared either by manual alkaline lysis or the Autogen protocol were digested with HindIII for analysis of restriction fragment sizes. This data were used to compare the extent of overlap among clones. Typically 1-2 μg were used for each reaction. Reaction mixtures included: 1X Buffer 2 (New England Biolabs), 0.1 mg/ml bovine serum albumin (New England Biolabs), 50 μg/ml RNase A (Boehringer Mannheim), and 20 units of HindIII (New England Biolabs) in a final volume of 25 μl. Digestions were incubated at 37°C for 4-6 hours. BAC DNA was also digested with NotI for estimation of insert size by CHEF gel analysis (see below). Reaction conditions were identical to those for HindIII except that 20 units of NotI were used. Six μl of 6X Ficoll loading buffer containing bromphenol blue and xylene cyanol was added prior to electrophoresis.

HindIII digests were analyzed on 0.6% agarose (Seakem, FMC Bioproducts) in 1X TBE containing 0.5 μg/ml ethidium bromide. Gels (20 cm X 25 cm) were electrophoresed in a Model A4 electrophoresis unit (Owl Scientific) at 50 volts for 20-24 hrs. Molecular weight size markers included undigested lambda DNA, HindIII digested lambda DNA, and HaeIII digested _X174 DNA. Molecular weight markers were heated at 65°C for 2 min. prior to loading the gel. Images were captured with a Kodak DC40 CCD camera and analyzed with Kodak 1D software.

NotI digests were analyzed on a CHEF DRII (BioRad) electrophoresis unit according to the manufacturer's recommendations. Briefly, 1% agarose gels (BioRad pulsed field grade) were prepared in 0.5X TBE, equilibrated for 30 minutes in the electrophoresis unit at 14°C, and electrophoresed at 6 volts/cm for 14 hrs with circulation. Switching times were ramped from 10 sec to 20 sec. Gels were stained after electrophoresis in 0.5 μg/ml ethidium bromide. Molecular weight markers included undigested lambda DNA, HindIII digested lambda DNA, lambda ladder PFG ladder, and low range PFG marker (all from New England Biolabs).

BAC DNA prepared either by the manual alkaline lysis or Autogen protocols were labeled for FISH analysis using a Bioprime labeling kit (BioRad) according to the manufacturer's recommendation with minor modifications. Approximately 200 ng of DNA was used for each 50 µl reaction. 3 µl were analyzed on a 2% agarose gel to determine the extent of labeling. Reactions were purified using a Sephadex G50 spin column prior to *in situ* hybridization. Metaphase FISH was performed as described (Ma et al, *Cytogenet. Cell Genet.*, 74:266-271 (1996)).

VI. BAC Endsequencing

The sequencing of BAC insert ends utilized DNA prepared by either of the two methods described above. The DYEnamic energy transfer primers and Dynamic Direct cycle sequencing kits from Amersham were used for sequencing reactions. Ready made sequencing mix including the M13 -40 forward sequencing primer was used (Catalog # US79730) for the T7 BAC vector terminus; ready made sequencing mix (Catalog # US79530) was mixed with the M13 -28 reverse sequencing primer (Catalog # US79339) for the SP6 BAC vector terminus. The sequencing reaction mixes included one of the four fluorescently labeled dye-primers, one of the four dideoxy termination mixes, dNTPs, reaction buffer, and Thermosequenase. For each BAC DNA sample, 3 µl of the BAC DNA sample was aliquoted to 4 PCR strip tubes. 2 µl of one of the four dye primer/termination mix combinations was then added to each of the four tubes. The tubes were then sealed and centrifuged briefly prior to PCR. Thermocycling conditions involved a 1 minute denaturation at 95°C, 15 second annealing at 45°C, and extension for 1 minute at 70°C for 35 total cycles. After cycling the plates were centrifuged briefly to collect all the liquid to the bottom of the tubes. 5 µl of sterile distilled and deionized H_2O was then added into each tube, the plates sealed and centrifuged briefly again. The four samples for each BAC were then pooled together. DNA was then precipitated by adding 1.5 µl of 7.5 M NH_4OAc and 100 µl of -20°C 100% ethanol to each tube. Samples were mixed by pipetting up and down once. The plates were then sealed and incubated on ice for 10 minutes. Plates were centrifuged in a table top Haraeus centrifuge at 4000 rpm (3,290 g) for 30 minutes at 4°C to recover the DNA. The supernatant was removed and excess liquid blotted onto paper towels. Pellets were washed by adding 100 µl of -20°C 70% ethanol into each

tube and recentrifuging at 4000 rpm (3,290 g) for 10 minutes at 4°C. The supernatant was removed and excess liquid again removed by blotting on a paper towel. Remaining traces of liquid were removed by placing the plates upside down over a paper towel and centrifuging only until the centrifuge reached 800 rpm. Samples were then air dried at room temperature for 30 min. Tubes were capped and stored dry at -20°C until electrophoresis. Immediately prior to electrophoresis the DNA was dissolved in 1.5 μl of Amersham loading dye. Plates were then sealed and centrifuged at 2000 rpm (825 g). The plates were then vortexed on a plate shaker for 1-2 minutes. Samples were then recentrifuged at 2000 rpm (825 g) briefly. Samples were then heated at 65°C for 2 min. and immediately placed on ice. Standard gel electrophoresis was performed on ABI 377 fluorescent sequencers according to the manufacturer's recommendation.

VII. Sub-cloning and Sequencing of HBM BAC DNA

The physical map of the Zmax1 gene region provides a set of BAC clones that contain within them the Zmax1 gene and the HBM gene. DNA sequencing of several of the BACs from the region has been completed. The DNA sequence data is a unique reagent that includes data that one skilled in the art can use to identify the Zmax1 gene and the HBM gene, or to prepare probes to identify the gene(s), or to identify DNA sequence polymorphisms that identify the gene(s).

BAC DNA was isolated according to one of two protocols, either a Qiagen purification of BAC DNA (Qiagen, Inc. as described in the product literature) or a manual purification which is a modification of the standard alkaline lysis/Cesium Chloride preparation of plasmid DNA (see e.g., Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1997)). Briefly for the manual protocol, cells were pelleted, resuspended in GTE (50 mM glucose, 25 mM Tris-Cl (pH 8), 10 mM EDTA) and lysozyme (50 mg/ml solution), followed by NaOH/SDS (1% SDS/0.2 N NaOH) and then an ice-cold solution of 3 M KOAc (pH 4.5-4.8). RnaseA was added to the filtered supernatant, followed by Proteinase K and 20% SDS. The DNA was then precipitated with isopropanol, dried and resuspended in TE (10 mM Tris, 1 mM EDTA (pH 8.0)). The BAC DNA was further purified by Cesium Chloride density gradient centrifugation (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1997)).

Following isolation, the BAC DNA was sheared hydrodynamically using an HPLC (Hengen, *Trends in Biochem. Sci.*, 22:273-274 (1997)) to an insert size of 2000-3000 bp. After shearing, the DNA was concentrated and separated on a standard 1% agarose gel. A single fraction, corresponding to the approximate size, was excised from the gel and purified by electroelution (Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring, NY (1989)).

The purified DNA fragments were then blunt-ended using T4 DNA polymerase. The blunt-ended DNA was then ligated to unique BstXI-linker adapters (5' GTCTTCACCACGGGG and 5' GTGGTGAAGAC in 100-1000 fold molar excess). These linkers were complimentary to the BstXI-cut pMPX vectors (constructed by the inventors), while the overhang was not self-complimentary. Therefore, the linkers would not concatemerize nor would the cut-vector religate itself easily. The linker-adapted inserts were separated from the unincorporated linkers on a 1% agarose gel and purified using GeneClean (BIO 101, Inc.). The linker-adapted insert was then ligated to a modified pBlueScript vector to construct a "shotgun" subclone library. The vector contained an out-of-frame lacZ gene at the cloning site which became in-frame in the event that an adapter-dimer is cloned, allowing these to be avoided by their blue-color.

All subsequent steps were based on sequencing by ABI377 automated DNA sequencing methods. Only major modifications to the protocols are highlighted. Briefly, the library was then transformed into DH5α competent cells (Life Technologies, Bethesda, MD, DH5α transformation protocol). It was assessed by plating onto antibiotic plates containing ampicillin and IPTG/Xgal. The plates were incubated overnight at 37°C. Successful transformants were then used for plating of clones and picking for sequencing. The cultures were grown overnight at 37°. DNA was purified using a silica bead DNA preparation (Ng et al, *Nucl. Acids Res.*, 24:5045-5047 (1996)) method. In this manner, 25 μg of DNA was obtained per clone.

These purified DNA samples were then sequenced using ABI dye-terminator chemistry. The ABI dye terminator sequence reads were run on ABI377 machines and the data was directly transferred to UNIX machines following lane tracking of

the gels. All reads were assembled using PHRAP (P. Green, Abstracts of DOE Human Genome Program Contractor-Grantee Workshop V, Jan. 1996, p.157) with default parameters and quality scores. The initial assembly was done at 6-fold coverage and yielded an average of 8-15 contigs. Following the initial assembly, missing mates (sequences from clones that only gave one strand reads) were identified and sequenced with ABI technology to allow the identification of additional overlapping contigs. Primers for walking were selected using a Genome Therapeutics program Pick_primer near the ends of the clones to facilitate gap closure. These walks were sequenced using the selected clones and primers. Data were reassembled with PHRAP into sequence contigs.

VIII. Gene Identification by Computational Methods

Following assembly of the BAC sequences into contigs, the contigs were subjected to computational analyses to identify coding regions and regions bearing DNA sequence similarity to known genes. This protocol included the following steps.

1. Degap the contigs: the sequence contigs often contain symbols (denoted by a period symbol) that represent locations where the individual ABI sequence reads have insertions or deletions. Prior to automated computational analysis of the contigs, the periods were removed. The original data was maintained for future reference.

2. BAC vector sequences were "masked" within the sequence by using the program cross match (Phil Green, http:\\chimera.biotech.washington.edu\UWGC). Since the shotgun libraries construction detailed above leaves some BAC vector in the shotgun libraries, this program was used to compare the sequence of the BAC contigs to the BAC vector and to mask any vector sequence prior to subsequent steps. Masked sequences were marked by an "X" in the sequence files, and remained inert during subsequent analyses.

3. *E. coli* sequences contaminating the BAC sequences were masked by comparing the BAC contigs to the entire *E. coli* DNA sequence.

4. Repetitive elements known to be common in the human genome were masked using cross match. In this implementation of crossmatch, the BAC

sequence was compared to a database of human repetitive elements (Jerzy Jerka, Genetic Information Research Institute, Palo Alto, CA). The masked repeats were marked by X and remained inert during subsequent analyses.

5. The location of exons within the sequence was predicted using the MZEF computer program (Zhang, *Proc. Natl. Acad. Sci.*, 94:565-568 (1997)).

6. The sequence was compared to the publicly available unigene database (National Center for Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; www.ncbi.nlm.nih.gov) using the blastn2 algorithm (Altschul et al, *Nucl. Acids Res.*, 25:3389-3402 (1997)). The parameters for this search were: E=0.05, v=50, B=50 (where E is the expected probability score cutoff, V is the number of database entries returned in the reporting of the results, and B is the number of sequence alignments returned in the reporting of the results (Altschul et al, *J. Mol. Biol.*, 215:403-410 (1990)).

7. The sequence was translated into protein for all six reading frames, and the protein sequences were compared to a non-redundant protein database compiled from Genpept Swissprot PIR (National Center for Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; www.ncbi.nlm.nih.gov). The parameters for this search were E=0.05, V=50, B= 50, where E, V, and B are defined as above.

8. The BAC DNA sequence was compared to the database of the cDNA clones derived from direct selection experiments (described below) using blastn2 (Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The parameters for this search were E=0.05, V=250, B=250, where E, V, and B are defined as above.

9. The BAC sequence was compared to the sequences of all other BACs from the HBM region on chromosome 11q12-13 using blastn2 (Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The parameters for this search were E=0.05, V=50, B=50, where E, V, and B are defined as above.

10. The BAC sequence was compared to the sequences derived from the ends of BACs from the HBM region on chromosome 11q12-13 using blastn2 (Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The parameters for this search were E=0.05, V=50, B=50, where E, V, and B are defined as above.

11. The BAC sequence was compared to the Genbank database (National Center for Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; www.ncbi.nlm.nih.gov) using blastn2 (Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The parameters for this search were E=0.05, V=50, B=50, where E, V, and B are defined as above.

12. The BAC sequence was compared to the STS division of Genbank database (National Center for Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; www.ncbi.nlm.nih.gov) using blastn2 (Altschul et al, 1997). The parameters for this search were E=0.05, V=50, B= 50, where E, V, and B are defined as above.

13. The BAC sequence was compared to the Expressed Sequence (EST) Tag Genbank database (National Center for Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; www.ncbi.nlm.nih.gov) using blastn2 (Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The parameters for this search were E=0.05, V=250, B=250, where E, V, and B are defined as above.

IX. Gene Identification by Direct cDNA Selection

Primary linkered cDNA pools were prepared from bone marrow, calvarial bone, femoral bone, kidney, skeletal muscle, testis and total brain. Poly (A) + RNA was prepared from calvarial and femoral bone tissue (Chomczynski et al, *Anal. Biochem.*, 162:156-159 (1987); D'Alessio et al, *Focus*, 9:1-4 (1987)) and the remainder of the mRNA was purchased from Clontech (Palo Alto, California). In order to generate oligo(dT) and random primed cDNA pools from the same tissue, 2.5 μg mRNA was mixed with oligo(dT) primer in one reaction and 2.5 μg mRNA was mixed with random hexamers in another reaction, and both were converted to first and second strand cDNA according to manufacturers recommendations (Life Technologies, Bethesda, MD). Paired phosphorylated cDNA linkers (see sequence below) were annealed together by mixing in a 1:1 ratio (10 μg each) incubated at 65°C for five minutes and allowed to cool to room temperature.

Paired linkers oligo1/2

OLIGO 1: 5'CTG AGC GGA ATT CGT GAG ACC3' (SEQ ID NO:12)

OLIGO 2: 5'TTG GTC TCA CGT ATT CCG CTC GA3' (SEQ ID NO:13)

Paired linkers oligo3/4

OLIGO 3: 5'CTC GAG AAT TCT GGA TCC TC3' (SEQ ID NO:14)

OLIGO 4: 5'TTG AGG ATC CAG AAT TCT CGA G3' (SEQ ID NO:15)

Paired linkers oligo5/6

OLIGO 5: 5'TGT ATG CGA ATT CGC TGC GCG3' (SEQ ID NO:16)

OLIGO 6: 5'TTC GCG CAG CGA ATT CGC ATA CA3' (SEQ ID NO:17)

Paired linkers oligo7/8

OLIGO 7: 5'GTC CAC TGA ATT CTC AGT GAG3' (SEQ ID NO:18)

OLIGO 8: 5'TTG TCA CTG AGA ATT CAG TGG AC3' (SEQ ID NO:19)

Paired linkers oligo11/12

OLIGO 11: 5'GAA TCC GAA TTC CTG GTC AGC3' (SEQ ID NO:20)

OLIGO 12: 5'TTG CTG ACC AGG AAT TCG GAT TC3' (SEQ ID NO:21)

Linkers were ligated to all oligo(dT) and random primed cDNA pools (see below) according to manufacturers instructions (Life Technologies, Bethesda, MD).

Oligo 1/2 was ligated to oligo(dT) and random primed cDNA pools prepared from bone marrow. Oligo 3/4 was ligated to oligo(dT) and random primed cDNA pools prepared from calvarial bone. Oligo 5/6 was ligated to oligo(dT) and random primed cDNA pools prepared from brain and skeletal muscle. Oligo 7/8 was ligated to oligo(dT) and random primed cDNA pools prepared from kidney. Oligo 11/12 was ligated to oligo(dT) and random primed cDNA pools prepared from femoral bone.

The cDNA pools were evaluated for length distribution by PCR amplification using 1 µl of a 1:1, 1:10, and 1:100 dilution of the ligation reaction, respectively. PCR reactions were performed in a Perkin Elmer 9600, each 25 µl volume reaction contained 1 µl of DNA, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 0.001% gelatin, 200 mM each dNTPs, 10 µM primer and 1 unit Taq DNA polymerase (Perkin Elmer) and was amplified under the following conditions:

30 seconds at 94°C, 30 seconds at 60°C and 2 minutes at 72°C for 30 cycles. The length distribution of the amplified cDNA pools were evaluated by electrophoresis on a 1% agarose gel. The PCR reaction that gave the best representation of the random primed and oligo(dT) primed cDNA pools was scaled up so that ~2-3 μg of each cDNA pool was produced. The starting cDNA for the direct selection reaction comprised of 0.5 μg of random primed cDNAs mixed with 0.5 μg of oligo(dT) primed cDNAs.

The DNA from the 54 BACs that were used in the direct cDNA selection procedure was isolated using Nucleobond AX columns as described by the manufacturer (The Nest Group, Inc.).

The BACs were pooled in equimolar amounts and 1 μg of the isolated genomic DNA was labeled with biotin 16-UTP by nick translation in accordance with the manufacturers instructions (Boehringer Mannheim). The incorporation of the biotin was monitored by methods that could be practiced by one skilled in the art (Del Mastro and Lovett, *Methods in Molecular Biology*, Humana Press Inc., NJ (1996)).

Direct cDNA selection was performed using methods that could be practiced by one skilled in the art (Del Mastro and Lovett, *Methods in Molecular Biology*, Humana Press Inc., NJ (1996)). Briefly, the cDNA pools were multiplexed in two separate reactions: In one reaction cDNA pools from bone marrow, calvarial bone, brain and testis were mixed, and in the other cDNA pools from skeletal muscle, kidney and femoral bone were mixed. Suppression of the repeats, yeast sequences and plasmid in the cDNA pools was performed to a Cot of 20. 100 ng of biotinylated BAC DNA was mixed with the suppressed cDNAs and hybridized in solution to a Cot of 200. The biotinylated DNA and the cognate cDNAs was captured on streptavidin-coated paramagnetic beads. The beads were washed and the primary selected cDNAs were eluted. These cDNAs were PCR amplified and a second round of direct selection was performed. The product of the second round of direct selection is referred to as the secondary selected material. A Galanin cDNA clone, previously shown to map to 11q12-13 (Evans, *Genomics*, 18:473-477 (1993)), was used to monitor enrichment during the two rounds of selection.

The secondary selected material from bone marrow, calvarial bone, femoral bone, kidney, skeletal muscle, testis and total brain was PCR amplified using modified primers of oligos 1, 3, 5, 7 and 11, shown below, and cloned into the UDG vector pAMP10 (Life Technologies, Bethesda, MD), in accordance with the manufacturer's recommendations.

Modified primer sequences:

Oligo1-CUA: 5'CUA CUA CUA CUA CTG AGC GGA ATT CGT GAG ACC3' (SEQ ID NO:22)

Oligo3-CUA: 5'CUA CUA CUA CUA CTC GAG AAT TCT GGA TCC TC3' (SEQ ID NO:23)

Oligo5-CUA: 5'CUA CUA CUA CUA TGT ATG CGA ATT CGC TGC GCG3' (SEQ ID NO:24)

Oligo7-CUA: 5'CUA CUA CUA CUA GTC CAC TGA ATT CTC AGT GAG3' (SEQ ID NO:25)

Oligo11-CUA: 5'CUA CUA CUA CUA GAA TCC GAA TTC CTG GTC AGC3' (SEQ ID NO:26)

The cloned secondary selected material, from each tissue source, was transformed into MAX Efficiency DH5a Competent Cells (Life Technologies, Bethesda, MD) as recommended by the manufacturer. 384 colonies were picked from each transformed source and arrayed into four 96 well microtiter plates. All secondarily selected cDNA clones were sequenced using M13 dye primer terminator cycle sequencing kit (Applied Biosystems), and the data collected by the ABI 377 automated fluorescence sequencer (Applied Biosystems). All sequences were analyzed using the BLASTN, BLASTX and FASTA programs (Altschul et al, *J. Mol. Biol.*, 215:403-410 (1990), Altschul et al, *Nucl. Acids. Res.*, 25:3389-3402 (1997)). The cDNA sequences were compared to a database containing sequences derived from human repeats, mitochondrial DNA, ribosomal

RNA, *E. coli* DNA to remove background clones from the dataset using the program cross_match. A further round of comparison was also performed using the program BLASTN2 against known genes (Genbank) and the BAC sequences from the HBM region. Those cDNAs that were >90% homologous to these sequences were filed according to the result and the data stored in a database for further analysis. cDNA sequences that were identified but did not have significant similarity to the BAC sequences from the HBM region or were eliminated by cross_match were hybridized to nylon membranes which contained the BACs from the HBM region, to ascertain whether they hybridized to the target.

Hybridization analysis was used to map the cDNA clones to the BAC target that selected them. The BACs that were identified from the HBM region were arrayed and grown into a 96 well microtiter plate. LB agar containing 25 µg/ml kanamycin was poured into 96 well microtiter plate lids. Once the agar had solidified, pre-cut Hybond N+ nylon membranes (Amersham) were laid on top of the agar and the BACs were stamped onto the membranes in duplicate using a hand held 96 well replica plater (V&P Scientific, Inc.). The plates were incubated overnight at 37°C. The membranes were processed according to the manufacturers recommendations.

The cDNAs that needed to be mapped by hybridization were PCR amplified using the relevant primer (oligos 1, 3, 5, 7 and 11) that would amplify that clone. For this PCR amplification, the primers were modified to contain a linkered digoxigenin molecule at the 5' of the oligonucleotide. The PCR amplification was performed under the same conditions as described in Preparation of cDNA Pools (above). The PCR products were evaluated for quality and quantity by electrophoresis on a 1% agarose gel by loading 5 µl of the PCR reaction. The nylon membranes containing the stamped BACs were individually pre-hybridized in 50 ml conical tubes containing 10 ml of hybridization solution (5x SSPE, 0.5x Blotto, 2.5% SDS and 1 mM EDTA (pH 8.0)). The 50 ml conical tubes were placed in a rotisserie oven (Robbins Scientific) for 2 hours at 65°C. Twenty-five ng of each cDNA probe was denatured and added into individual 50 ml conical tubes containing the nylon membrane and hybridization solution. The hybridization was performed overnight at 65°C. The filters were washed for 20 minutes at 65°C in

each of the following solutions: 3x SSPE, 0.1% SDS; 1x SSPE, 0.1% SDS and 0.1x SSPE, 0.1% SDS.

The membranes were removed from the 50 ml conical tubes and placed in a dish. Acetate sheets were placed between each membrane to prevent them from sticking to each other. The incubation of the membranes with the Anti-DIG-AP and CDP-Star was performed according to manufacturers recommendations (Boehringer Mannheim). The membranes were wrapped in Saran wrap and exposed to Kodak Bio-Max X-ray film for 1 hour.

X. cDNA Cloning and Expression Analysis

To characterize the expression of the genes identified by direct cDNA selection and genomic DNA sequencing in comparison to the publicly available databases, a series of experiments were performed to further characterize the genes in the HBM region. First, oligonucleotide primers were designed for use in the polymerase chain reaction (PCR) so that portions of a cDNA, EST, or genomic DNA could be amplified from a pool of DNA molecules (a cDNA library) or RNA population (RT-PCR and RACE). The PCR primers were used in a reaction containing genomic DNA to verify that they generated a product of the size predicted based on the genomic (BAC) sequence. A number of cDNA libraries were then examined for the presence of the specific cDNA or EST. The presence of a fragment of a transcription unit in a particular cDNA library indicates a high probability that additional portions of the same transcription unit will be present as well.

A critical piece of data that is required when characterizing novel genes is the length, in nucleotides, of the processed transcript or messenger RNA (mRNA). One skilled in the art primarily determines the length of an mRNA by Northern blot hybridization (Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor NY (1989)). Groups of ESTs and direct-selected cDNA clones that displayed significant sequence similarity to sequenced BACs in the critical region were grouped for convenience into approximately 30 kilobase units. Within each 30 kilobase unit there were from one up to fifty ESTs and direct-selected cDNA clones which comprised one or more independent transcription units. One or more ESTs or direct-selected cDNAs were

used as hybridization probes to determine the length of the mRNA in a variety of tissues, using commercially available reagents (Multiple Tissue Northern blot; Clontech, Palo Alto, California) under conditions recommended by the manufacturer.

Directionally cloned cDNA libraries from femoral bone, and calvarial bone tissue were constructed by methods familiar to one skilled in the art (for example, Soares in *Automated DNA Sequencing and Analysis*, Adams, Fields and Venter, Eds., Academic Press, NY, pages 110-114 (1994)). Bones were initially broken into fragments with a hammer, and the small pieces were frozen in liquid nitrogen and reduced to a powder in a tissue pulverizer (Spectrum Laboratory Products). RNA was extracted from the powdered bone by homogenizing the powdered bone with a standard Acid Guanidinium Thiocyanate-Phenol-Chloroform extraction buffer (e.g. Chomczynski and Sacchi, *Anal. Biochem.*, 162:156-159 (1987)) using a polytron homogenizer (Brinkman Instruments). Additionally, human brain and lung total RNA was purchased from Clontech. PolyA RNA was isolated from total RNA using dynabeads-dT according to the manufacturer's recommendations (Dynal, Inc.).

First strand cDNA synthesis was initiated using an oligonucleotide primer with the sequence: 5'-AACTGGAAGAATTC<u>GCGGCCGC</u>AGGAATTTTTTTTT TTTTTTTTT-3' (SEQ ID NO:27). This primer introduces a NotI restriction site (underlined) at the 3' end of the cDNA. First and second strand synthesis were performed using the "one-tube" cDNA synthesis kit as described by the anufacturer (Life Technologies, Bethesda, MD). Double stranded cDNAs were treated with T4 polynucleotide kinase to ensure that the ends of the molecules were blunt (Soares in *Automated DNA Sequencing and Analysis*, Adams, Fields and Venter, Eds., Academic Press, NY, pages 110-114 (1994)), and the blunt ended cDNAs were then size selected by a Biogel column (Huynh et al in *DNA Cloning*, Vol. 1, Glover, Ed., IRL Press, Oxford, pages 49-78 (1985)) or with a size-sep 400 sepharose column (Pharmacia, catalog # 27-5105-01). Only cDNAs of 400 base pairs or longer were used in subsequent steps. EcoRI adapters (sequence: 5' OH-AATTCGGCACGAG-OH 3' (SEQ ID NO:28), and 5' p-CTCGTGCCG-OH 3' (SEQ ID NO:29)) were then ligated to the double stranded cDNAs by methods familiar to one skilled in the art (Soares, 1994). The EcoRI adapters were then

removed from the 3' end of the cDNA by digestion with NotI (Soares, 1994). The cDNA was then ligated into the plasmid vector pBluescript II KS+ (Stratagene, La Jolla, California), and the ligated material was transformed into *E. coli* host DH10B or DH12S by electroporation methods familiar to one skilled in the art (Soares, 1994). After growth overnight at 37°C, DNA was recovered from the *E. coli* colonies after scraping the plates by processing as directed for the Mega-prep kit (Qiagen, Chatsworth, California). The quality of the cDNA libraries was estimated by counting a portion of the total numbers of primary transformants and determining the average insert size and the percentage of plasmids with no cDNA insert. Additional cDNA libraries (human total brain, heart, kidney, leukocyte, and fetal brain) were purchased from Life Technologies, Bethesda, MD.

cDNA libraries, both oligo (dT) and random hexamer (N_6) primed, were used for isolating cDNA clones transcribed within the HBM region: human bone, human brain, human kidney and human skeletal muscle (all cDNA libraries were made by the inventors, except for skeletal muscle (dT) and kidney (dT) cDNA libraries). Four 10 x 10 arrays of each of the cDNA libraries were prepared as follows: the cDNA libraries were titered to 2.5 x 10^6 using primary transformants. The appropriate volume of frozen stock was used to inoculate 2 L of LB/ampicillin (100 mg/ml). This inoculated liquid culture was aliquotted into 400 tubes of 4 ml each. Each tube contained approximately 5000 cfu. The tubes were incubated at 30°C overnight with gentle agitation. The cultures were grown to an OD of 0.7-0.9. Frozen stocks were prepared for each of the cultures by aliquotting 100 μl of culture and 300 μl of 80% glycerol. Stocks were frozen in a dry ice/ethanol bath and stored at -70°C. The remaining culture was DNA prepared using the Qiagen (Chatsworth, CA) spin miniprep kit according to the manufacturer's instructions. The DNAs from the 400 cultures were pooled to make 80 column and row pools. The cDNA libraries were determined to contain HBM cDNA clones of interest by PCR. Markers were designed to amplify putative exons. Once a standard PCR optimization was performed and specific cDNA libraries were determined to contain cDNA clones of interest, the markers were used to screen the arrayed library. Positive addresses indicating the presence of cDNA clones were confirmed by a second PCR using the same markers.

Once a cDNA library was identified as likely to contain cDNA clones corresponding to a specific transcript of interest from the HBM region, it was manipulated to isolate the clone or clones containing cDNA inserts identical to the EST or direct-selected cDNA of interest. This was accomplished by a modification of the standard "colony screening" method (Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor NY (1989)). Specifically, twenty 150 mm LB+ampicillin agar plates were spread with 20,000 colony forming units (cfu) of cDNA library and the colonies allowed to grow overnight at 37°C. Colonies were transferred to nylon filters (Hybond from Amersham, or equivalent) and duplicates prepared by pressing two filters together essentially as described (Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor NY (1989)). The "master" plate was then incubated an additional 6-8 hours to allow the colonies to grow back. The DNA from the bacterial colonies was then affixed to the nylon filters by treating the filters sequentially with denaturing solution (0.5 N NaOH, 1.5 M NaCl) for two minutes, neutralization solution (0.5 M Tris-Cl pH 8.0, 1.5 M NaCl) for two minutes (twice). The bacterial colonies were removed from the filters by washing in a solution of 2X SSC/0.1% SDS for one minute while rubbing with tissue paper. The filters were air dried and baked under vacuum at 80°C for 1-2 hours.

A cDNA hybridization probe was prepared by random hexamer labeling (Fineberg and Vogelstein, *Anal. Biochem.*, 132:6-13 (1983)) or by including gene-specific primers and no random hexamers in the reaction (for small fragments). Specific activity was calculated and was $>5X10^8$ cpm/10^8 μg of cDNA. The colony membranes were then prewashed in 10 mM Tris-Cl pH 8.0, 1 M NaCl, 1 mM EDTA, 0.1% SDS for 30 minutes at 55°C. Following the prewash, the filters were prehybridized in > 2 ml/filter of 6X SSC, 50 % deionized formamide, 2% SDS, 5X Denhardt's solution, and 100 mg/ml denatured salmon sperm DNA, at 42°C for 30 minutes. The filters were then transferred to hybridization solution (6X SSC, 2% SDS, 5X Denhardt's, 100 mg/ml denatured salmon sperm DNA) containing denatured α^{32}P-dCTP-labeled cDNA probe and incubated at 42°C for 16-18 hours.

After the 16-18 hour incubation, the filters were washed under constant agitation in 2X SSC, 2% SDS at room temperature for 20 minutes, followed by two

washes at 65°C for 15 minutes each. A second wash was performed in 0.5 X SSC, 0.5% SDS for 15 minutes at 65°C. Filters were then wrapped in plastic wrap and exposed to radiographic film for several hours to overnight. After film development, individual colonies on plates were aligned with the autoradiograph so that they could be picked into a 1 ml solution of LB Broth containing ampicillin. After shaking at 37°C for 1-2 hours, aliquots of the solution were plated on 150 mm plates for secondary screening. Secondary screening was identical to primary screening (above) except that it was performed on plates containing ~250 colonies so that individual colonies could be clearly identified for picking.

After colony screening with radiolabeled probes yielded cDNA clones, the clones were characterized by restriction endonuclease cleavage, PCR, and direct sequencing to confirm the sequence identity between the original probe and the isolated clone. To obtain the full-length cDNA, the novel sequence from the end of the clone identified was used to probe the library again. This process was repeated until the length of the cDNA cloned matches that estimated to be full-length by the northern blot analysis.

RT-PCR was used as another method to isolate full length clones. The cDNA was synthesized and amplified using a "Superscript One Step RT-PCR" kit (Life Technologies, Gaithersburg, MD). The procedure involved adding 1.5 μg of RNA to the following: 25 μl of reaction mix provided which is a proprietary buffer mix with $MgSO_4$ and dNTP's, 1 μl sense primer (10 μM) and 1 μl anti-sense primer (10 μM), 1 μl reverse transcriptase and Taq DNA polymerase mix provided and autoclaved water to a total reaction mix of 50 μl. The reaction was then placed in a thermocycler for 1 cycle at 50°C for 15 to 30 minutes, then 94°C for 15 seconds, 55-60°C for 30 seconds and 68-72°C for 1 minute per kilobase of anticipated product and finally 1 cycle of 72°C for 5-10 minutes. The sample was analyzed on an agarose gel. The product was excised from the gel and purified from the gel (GeneClean, Bio 101). The purified product was cloned in pCTNR (General Contractor DNA Cloning System, 5 Prime - 3 Prime, Inc.) and sequenced to verify that the clone was specific to the gene of interest.

Rapid Amplification of cDNA ends (RACE) was performed following the manufacturer's instructions using a Marathon cDNA Amplification Kit (Clontech,

Palo Alto, CA) as a method for cloning the 5' and 3' ends of candidate genes. cDNA pools were prepared from total RNA by performing first strand synthesis, where a sample of total RNA sample was mixed with a modified oligo (dT) primer, heated to 70°C, cooled on ice and followed by the addition of: 5x first strand buffer, 10 mM dNTP mix, and AMV Reverse Transcriptase (20 U/μl). The tube was incubated at 42°C for one hour and then the reaction tube was placed on ice. For second strand synthesis, the following components were added directly to the reaction tube: 5x second strand buffer, 10 mM dNTP mix, sterile water, 20x second strand enzyme cocktail and the reaction tube was incubated at 16°C for 1.5 hours. T4 DNA Polymerase was added to the reaction tube and incubated at 16°C for 45 minutes. The second-strand synthesis was terminated with the addition of an EDTA/Glycogen mix. The sample was subjected to a phenol/chloroform extraction and an ammonium acetate precipitation. The cDNA pools were checked for quality by analyzing on an agarose gel for size distribution. Marathon cDNA adapters (Clontech) were then ligated onto the cDNA ends. The specific adapters contained priming sites that allowed for amplification of either 5' or 3' ends, depending on the orientation of the gene specific primer (GSP) that was chosen. An aliquot of the double stranded cDNA was added to the following reagents: 10 μM Marathon cDNA adapter, 5x DNA ligation buffer, T4 DNA ligase. The reaction was incubated at 16°C overnight. The reaction was heat inactivated to terminate the reaction. PCR was performed by the addition of the following to the diluted double stranded cDNA pool: 10x cDNA PCR reaction buffer, 10 μM dNTP mix, 10 μM GSP, 10 μM AP1 primer (kit), 50x Advantage cDNA Polymerase Mix. Thermal Cycling conditions were 94°C for 30 seconds, 5 cycles of 94°C for 5 seconds, 72°C for 4 minutes, 5 cycles of 94°C for 5 seconds, 70°C for 4 minutes, 23 cycles of 94°C for 5 seconds, 68°C for 4 minutes. After the first round of PCR was performed using the GSP to extend to the end of the adapter to create the adapter primer binding site, exponential amplification of the specific cDNA of interest was observed. Usually a second nested PCR is performed to confirm the specific cDNA. The RACE product was analyzed on an agarose gel and then excised and purified from the gel (GeneClean, BIO 101). The RACE product was then cloned into pCTNR (General Contractor

DNA Cloning System, 5' - 3', Inc.) and the DNA sequence determined to verify that the clone is specific to the gene of interest.

XI. Mutation Analysis

Comparative genes were identified using the above procedures and the exons from each gene were subjected to mutation detection analysis. Comparative DNA sequencing was used to identify polymorphisms in HBM candidate genes from chromosome 11q12-13. DNA sequences for candidate genes were amplified from patient lymphoblastoid cell lines.

The inventors developed a method based on analysis of direct DNA sequencing of PCR products amplified from candidate regions to search for the causative polymorphism. The procedure consisted of three stages that used different subsets of HBM family to find segregating polymorphisms and a population panel to assess the frequency of the polymorphisms. The family resources result from a single founder leading to the assumption that all affected individuals will share the same causative polymorphism.

Candidate regions were first screened in a subset of the HBM family consisting of the proband, daughter, and her mother, father and brother. Monochromosomal reference sequences were produced concurrently and used for comparison. The mother and daughter carried the HBM polymorphism in this nuclear family, providing the ability to monitor polymorphism transmission. The net result is that two HBM chromosomes and six non-HBM chromosomes were screened. This allowed exclusion of numerous frequent alleles. Only alleles exclusively present in the affected individuals passed to the next level of analysis.

Polymorphisms that segregated exclusively with the HBM phenotype in this original family were then re-examined in an extended portion of the HBM pedigree consisting of two additional nuclear families. These families consisted of five HBM and three unaffected individuals. The HBM individuals in this group included the two critical crossover individuals, providing the centromeric and telomeric boundaries of the critical region. Tracking the heredity of polymorphisms between these individuals and their affected parents allowed for further refining of the critical region. This group brought the total of HBM chromosomes screened to seven and the total of non-HBM chromosomes to seventeen.

When a given polymorphism continued to segregate exclusively with the HBM phenotype in the extended group, a population panel was then examined. This panel of 84 persons consisted of 42 individuals known to have normal bone mineral density and 42 individuals known to be unrelated but with untyped bone mineral density. Normal bone mineral density is within two standard deviations of BMD Z score 0. The second group was from the widely used CEPH panel of individuals. Any segregating polymorphisms found to be rare in this population were subsequently examined on the entire HBM pedigree and a larger population.

Polymerase chain reaction (PCR) was used to generate sequencing templates from the HBM family's DNA and monochromosomal controls. Enzymatic amplification of genes within the HBM region on 11q12-13 was accomplished using the PCR with oligonucleotides flanking each exon as well as the putative 5' regulatory elements of each gene. The primers were chosen to amplify each exon as well as 15 or more base pairs within each intron on either side of the splice. All PCR primers were made as chimeras to facilitate dye primer sequencing. The M13-21F (5'- GTA A CGA CGG CCA GT -3') (SEQ ID NO:30) and -28REV (5'- AAC AGC TAT GAC CAT G -3') (SEQ ID NO:31) primer binding sites were built on to the 5' end of each forward and reverse PCR primer, respectively, during synthesis. 150 ng of genomic DNA was used in a 50 μl PCR with 2 U AmpliTaq, 500 nM primer and 125 μM dNTP. Buffer and cycling conditions were specific to each primer set. TaqStart antibody (Clontech) was used for hot start PCR to minimize primer dimer formation. 10% of the product was examined on an agarose gel. The appropriate samples were diluted 1:25 with deionized water before sequencing.

Each PCR product was sequenced according to the standard Energy Transfer primer (Amersham) protocol. All reactions took place in 96 well trays. 4 separate reactions, one each for A, C, G and T were performed for each template. Each reaction included 2 μl of the sequencing reaction mix and 3 μl of diluted template. The plates were then heat sealed with foil tape and placed in a thermal cycler and cycled according to the manufacturer's recommendation. After cycling, the 4 reactions were pooled. 3 μl of the pooled product was transferred to a new 96 well plate and 1 μl of the manufacturer's loading dye was added to each well. All 96 well pipetting procedures occurred on a Hydra 96 pipetting station (Robbins Scientific,

USA). 1 µl of pooled material was directly loaded onto a 48 lane gel running on an ABI 377 DNA sequencer for a 10 hour, 2.4 kV run.

Polyphred (University of Washington) was used to assemble sequence sets for viewing with *Consed* (University of Washington). Sequences were assembled in groups representing all relevant family members and controls for a specified target region. This was done separately for each of the three stages. Forward and reverse reads were included for each individual along with reads from the monochromosomal templates and a color annotated reference sequence. *Polyphred* indicated potential polymorphic sites with a purple flag. Two readers independently viewed each assembly and assessed the validity of the purple-flagged sites.

A total of 23 exons present in the mature mRNA and several other portions of the primary transcript were evaluated for heterozygosity in the nuclear family of two HBM-affected and two unaffected individuals. 25 SNPs were identified, as shown in the table below.

TABLE 4: Single Nucleotide Polymorphisms in the Zmax1 Gene and Environs

Exon Name	Location	Base Change
b200e21-h_Contig1_1.nt	69169 (309G)	C/A
b200e21-h_Contig4_12.nt	27402 (309G)	A/G
b200e21-h_Contig4_13.nt	27841 (309G)	T/C
b200e21-h_Contig4_16.nt	35600 (309G)	A/G
b200e21-h_Contig4_21.nt	45619 (309G)	G/A
b200e21-h_Contig4_22.nt-a	46018 (309G)	T/G
b200e21-h_Contig4_22.nt-b	46093 (309G)	T/G
b200e21-h_Contig4_22.nt-c	46190 (309G)	A/G
b200e21-h_Contig4_24.nt-a	50993 (309G)	T/C
b200e21-h_Contig4_24.nt-b	51124 (309G)	C/T
b200e21-h_Contig4_25.nt	55461 (309G)	C/T
b200e21-h_Contig4_33.nt-a	63645 (309G)	C/A
b200e21-h_Contig4_33.nt-b	63646 (309G)	A/C
b200e21-h_Contig4_61.nt	24809 (309G)	T/G
b200e21-h_Contig4_62.nt	27837 (309G)	T/C

Exon Name	Location	Base Change
b200e21-h_Contig4_63.nt-a	31485 (309G)	C/T
b200e21-h_Contig4_63.nt-b	31683 (309G)	A/G
b200e21-h_Contig4_9.nt	24808 (309G)	T/G
b527d12-h_Contig030g_1.nt-a	31340 (308G)	T/C
b527d12-h_Contig030g_1.nt-b	32538 (308G)	A/G
b527d12-h_Contig080C_2.nt	13224 (308G)	A/G
b527d12-h_Contig087C_1.nt	21119 (308G)	C/A
b527d12-h_Contig087C_4.nt	30497 (308G)	G/A
b527d12-h_Contig088C_4.nt	24811 (309G)	A/C
b527d12-h_Contig089_1HP.nt	68280 (309G)	G/A

In addition to the polymorphisms presented in Table 4, two additional polymorphisms can also be present in SEQ ID NO:2. These is a change at position 2002 of SEQ ID NO:2. Either a guanine or an adenine can appear at this position. This polymorphism is silent and is not associated with any change in the amino acid sequence. The second change is at position 4059 of SEQ ID NO:2 corresponding in a cytosine (C) to thymine (T) change. This polymorphism results in a corresponding amino acid change from a valine (V) to an alanine (A). Other polymorphisms were found in the candidate gene exons and adjacent intron sequences. Any one or combination of the polymorphisms listed in Table 4 or the two discussed above could also have a minor effect on bone mass when present in SEQ ID NO:2.

The present invention encompasses the nucleic acid sequences having the nucleic acid sequence of SEQ ID NO: 1 with the above-identified point mutations.

Preferably, the present invention encompasses the nucleic acid of SEQ ID NO: 2. Specifically, a base-pair substitution changing G to T at position 582 in the coding sequence of Zmax1 (the HBM gene) was identified as heterozygous in all HBM individuals, and not found in the unaffected individuals (i.e., b527d12-h_Contig087C_1.nt). Fig. 5 shows the order of the contigs in B527D12. The direction of transcription for the HBM gene is from left to right. The sequence of contig308G of B527D12 is the reverse complement of the coding region to the

HBM gene. Therefore, the relative polymorphism in contig 308G shown in Table 4 as a base change substitution of C to A is the complement to the G to T substitution in the HBM gene. This mutation causes a substitution of glycine 171 with valine (G171V).

The HBM polymorphism was confirmed by examining the DNA sequence of different groups of individuals. In all members of the HBM pedigree (38 individuals), the HBM polymorphism was observed in the heterozygous form in affected (i.e., elevated bone mass) individuals only (N=18). In unaffected relatives (N=20) (BMDZ<2.0) the HBM polymorphism was never observed. To determine whether this polymorphism was ever observed in individuals outside of the HBM pedigree, 297 phenotyped individuals were characterized at the site of the HBM gene. None were heterozygous at the site of the HBM polymorphism. In an unphenotyped control group, none of 64 individuals were observed to be heterozygous at position 582. Taken together, these data prove that the polymorphism observed in the kindred displaying the high bone mass phenotype is strongly correlated with the G→T polymorphism at position 582 of Zmax1. Furthermore, these results coupled with the ASO results described below, establish that the HBM polymorphism genetically segregates with the HBM phenotype, and that both the HBM polymorphism and phenotype are rare in the general population.

XII. Allele Specific Oligonucleotide (ASO) Analysis

The amplicon containing the HBM1 polymorphism was PCR amplified using primers specific for the exon of interest. The appropriate population of individuals was PCR amplified in 96 well microtiter plates as follows. PCR reactions (20 μl) containing 1X Promega PCR buffer (Cat. # M1883 containing 1.5 mM $MgCl_2$), 100mM dNTP, 200 nM PCR primers (1863F: CCAAGTTCTGAGAAGTCC and 1864R: AATACCTGAAACCATACCTG), 1 U Amplitaq, and 20 ng of genomic DNA were prepared and amplified under the following PCR conditions: 94°C, 1 minute, (94°C, 30 sec.; 58°C, 30 sec.; 72°C, 1 min.) X35 cycles), 72°C, 5', 4°C, hold. Loading dye was then added and 10 μl of the products was electrophoresed on 1.5% agarose gels containing 1 μg/ml ethidium bromide at 100-150 V for 5-10 minutes. Gels were treated 20 minutes in denaturing

solution (1.5 M NaCl, 0.5 N NaOH), and rinsed briefly with water. Gels were then neutralized in 1 M Tris-HCl, pH 7.5, 1.5 M NaCl, for 20 minutes and rinsed with water. Gels were soaked in 10 X SSC for 20 minutes and blotted onto nylon transfer membrane (Hybond N+- Amersham) in 10X SSC overnight. Filters were the rinsed in 6X SSC for 10 minutes and UV crosslinked.

The allele specific oligonucleotides (ASO) were designed with the polymorphism approximately in the middle. Oligonucleotides were phosphate free at the 5'end and were purchased from Gibco BRL. Sequences of the oligonucleotides are:

2326 Zmax1.ASO.g: AGACTGGG<u>G</u>TGAGACGC

2327 Zmax1.ASO.t: CAGACTGGG<u>T</u>TGAGACGCC

The polymorphic nucleotides are underlined. To label the oligos, 1.5 μl of 1 μg/μl ASO oligo (2326.Zmax1.ASO.g or 2327.Zmax1.ASO.t), 11 μl ddH_2O, 2 μl 10X kinase forward buffer, 5 μl $\gamma^{32}P$-ATP (6000 Ci/mMole), and 1 μl T4 polynucleotide kinase (10 U/μl) were mixed, and the reaction incubated at 37°C for 30-60 minutes. Reactions were then placed at 95°C for 2 minutes and 30 ml H_2O was added. The probes were purified using a G25 microspin column (Pharmacia).

Blots were prehybridized in 10 ml 5X SSPE, 5X Denhardt's, 2% SDS, and 100 μg/ml, denatured, sonicated salmon sperm DNA at 40°C for 2 hr. The entire reaction mix of kinased oligo was then added to 10 ml fresh hybridization buffer (5X SSPE, 5X Denhardt's, 2% SDS) and hybridized at 40°C for at least 4 hours to overnight.

All washes done in 5X SSPE, 0.1 % SDS. The first wash was at 45°C for 15 minutes; the solution was then changed and the filters washed 50°C for 15 minutes. Filters were then exposed to Kodak biomax film with 2 intensifying screens at –70°C for 15 minutes to 1 hr. If necessary the filters were washed at 55°C for 15 minutes and exposed to film again. Filters were stripped by washing in boiling 0.1X SSC, 0.1% SDS for 10 minutes at least 3 times.

The two films that best captured the allele specific assay with the 2 ASOs were converted into digital images by scanning them into Adobe PhotoShop. These

images were overlaid against each other in Graphic Converter and then scored and stored in FileMaker Pro 4.0 (see Fig. 9).

In order to determine the HBM1 allele frequency in ethnically diverse populations, 672 random individuals from various ethnic groups were typed by the allele specific oligonucleotide (ASO) method. This population included 96 CEPH grandparents (primarily Caucasian), 192 Caucasian, 192 African-American, 96 Hispanic, and 96 Asian individuals. No evidence was obtained for the presence of the HBM1 polymorphism in any of these individuals. Overall, a total of 911 individuals were typed either by direct sequencing or ASO hybridization; all were homozygous GG at the site of the HBM polymorphism (Fig. 14). This information illustrates that the HBM1 allele is rare in various ethnic populations.

Thus this invention provides a rapid method of identifying individuals with the HBM1 allele. This method could be used in the area of diagnostics and screening of an individual for susceptibility to osteoporosis or other bone disorder. The assay could also be used to identify additional individuals with the HBM1 allele or the additional polymorphisms described herein.

XIII. Cellular Localization of Zmax1

A. Gene Expression in Rat tibia by non isotopic In Situ Hybridization

In situ hybridization was conducted by Pathology Associates International (PAI), Frederick, MD. This study was undertaken to determine the specific cell types that express the Zmax1 gene in rat bone with particular emphasis on areas of bone growth and remodeling. Zmax1 probes used in this study were generated from both human (HuZmax1) and mouse (MsZmax1) cDNAs, which share an 87% sequence identity. The homology of human and mouse Zmax1 with rat Zmax1 is unknown.

For example, gene expression by non-isotopic *in situ* hybridization was performed as follows, but other methods would be known to the skilled artisan. Tibias were collected from two 6 to 8 week old female Sprague Dawley rats

euthanized by carbon dioxide asphyxiation. Distal ends were removed and proximal tibias were snap frozen in OCT embedding medium with liquid nitrogen immediately following death. Tissues were stored in a –80°C freezer.

Probes for amplifying PCR products from cDNA were prepared as follows. The primers to amplify PCR products from a cDNA clone were chosen using published sequences of both human LRP5 (Genbank Accession No. ABO17498) and mouse LRP5 (Genbank Accession No. AFO64984). In order to minimize cross reactivity with other genes in the LDL receptor family, the PCR products were derived from an intracellular portion of the protein coding region. PCR was performed in a 50 μl reaction volume using cDNA clone as template. PCR reactions contained 1.5 mM $MgCl_2$, 1 unit Amplitaq, 200 μM dNTPs and 2 μM each primer. PCR cycling conditions were 94°C for 1 min., followed by 35 cycles of 94°C for 30 seconds, 55°C for 30 seconds, 72°C for 30 seconds; followed by a 5 minute extension at 72°C. The reactions were then run on a 1.5% agarose Tris-Acetate gel. DNA was eluted from the agarose, ethanol precipitated and resuspended in 10 mM Tris, pH 8.0. Gel purified PCR products were prepared for both mouse and human cDNAs and supplied to Pathology Associates International for *in situ* hybridizations.

The sequence of the human and mouse PCR primers and products were as follows:

<u>Human Zmax 1 sense primer (HBM1253)</u>

CCCGTGTGCTCCGCCGCCCAGTTC

<u>Human Zmax 1 antisense primer (HBM1465)</u>

GGCTCACGGAGCTCATCATGGACTT

<u>Human Zmax1 PCR product</u>

CCCGTGTGCTCCGCCGCCCAGTTCCCCTGCGCGCGGGGTCAGTGTGTGGA
CCTGCGCCTGCGCTGCGACGGCGAGGCAGACTGTCAGGACCGCTCAGAC

GAGGTGGACTGTGACGCCATCTGCCTGCCCAACCAGTTCCGGTGTGCGA
GCGGCCAGTGTGTCCTCATCAAACAGCAGTGCGACTCCTTCCCCGACTGT
ATCGACGGCTCCGACGAGCTCATGTGTGAAATCACCAAGCCGCCCTCAG
ACGACAGCCCGGCCCACAGCAGTGCCATCGGGCCCGTCATTGGCATCAT
CCTCTCTCTCTTCGTCATGGGTGGTGTCTATTTTGTGTGCCAGCGCGTGGT
GTGCCAGCGCTATGCGGGGGCCAACGGGCCCTTCCCGCACGAGTATGTC
AGCGGGACCCCGCACGTGCCCCTCAATTTCATAGCCCCGGGCGGTTCCC
AGCATGGCCCCTTCACAGGCATCGCATGCGGAAAGTCCATGATGAGCTC
CGTGAGCC

Mouse Zmax 1 Sense primer (HBM1655)

AGCGAGGCCACCATCCACAGG

Mouse Zmax 1 antisense primer (HBM1656)

TCGCTGGTCGGCATAATCAAT

Mouse Zmax1 PCR product

AGCAGAGCCACCATCCACAGGATCTCCCTGGAGACTAACAACAACGATG
TGGCTATCCCACTCACGGGTGTCAAAGAGGCCTCTGCACTGGACTTTGAT
GTGTCCAACAATCACATCTACTGGACTGATGTTAGCCTCAAGACGATCA
GCCGAGCCTTCATGAATGGGAGCTCAGTGGAGCACGTGATTGAGTTTGG
CCTCGACTACCCTGAAGGAATGGCTGTGGACTGGATGGGCAAGAACCTC
TATTGGGCGGACACAGGGACCAACAGGATTGAGGTGGCCCGGCTGGATG
GGCAGTTCCGGCAGGTGCTTGTGTGGAGAGACCTTGACAACCCCAGGTC
TCTGGCTCTGGATCCTACTAAAGGCTACATCTACTGGACTGAGTGGGGTG
GCAAGCCAAGGATTGTGCGGGCCTTCATGGATGGGACCAATTGTATGAC
ACTGGTAGACAAGGTGGGCCGGGCCAACGACCTCACCATTGATTATGCC
GACCAGCGA

Riboprobes were synthesized as follows. The PCR products were reamplified with chimeric primers designed to incorporate either a T3 promoter upstream, or a T7 promoter downstream of the reamplification products. The resulting PCR products were used as template to synthesize digoxigenin-labeled riboprobes by *in vitro* transcription (IVT). Antisense and sense riboprobes were synthesized using T7 and T3 RNA polymerases, respectively, in the presence of digoxigenin-11-UTP (Boehringer-Mannheim) using a MAXIscript IVT kit (Ambion) according to the manufacturer. The DNA was then degraded with Dnase-1, and unincorporated digoxigenin was removed by ultrafiltration. Riboprobe integrity was assessed by electrophoresis through a denaturing polyacrylamide gel. Molecular size was compared with the electrophoretic mobility of a 100–1000 base pair (bp) RNA ladder (Ambion). Probe yield and labeling was evaluated by blot immunochemistry. Riboprobes were stored in 5 µl aliquots at –80°C.

The *in situ* hybridization was performed as follows. Frozen rat bone was cut into 5 µM sections on a Jung CM3000 cryostat (Leica) and mounted on adhesive slides (Instrumedics). Sections were kept in the cryostat at –20°C until all the slides were prepared in order to prevent mRNA degradation prior to post-fixation for 15 minutes in 4% paraformaldehyde. Following post-fixation, sections were incubated with 1 ng/µl of either antisense or sense riboprobe in Pathology Associates International (PAI) customized hybridization buffer for approximately 40 hours at 58°C. Following hybridization, slides were subjected to a series of post-hybridization stringency washes to reduce nonspecific probe binding. Hybridization was visualized by immunohistochemistry with an anti-digoxigenin antibody (FAB fragment) conjugated to alkaline phosphatase. Nitroblue tetrazolium chloride/bromochloroindolyl phosphate (Boehringer-Mannheim), a precipitating alkaline phosphatase substrate, was used as the chromogen to stain hybridizing cells

purple to nearly black, depending on the degree of staining. Tissue sections were counter-stained with nuclear fast red. Assay controls included omission of the probe, omission of probe and anti-digoxigenin antibody.

Specific cell types were assessed for demonstration of hybridization with antisense probes by visualizing a purple to black cytoplasmic and/or peri-nuclear staining indicating a positive hybridization signal for mRNA. Each cell type was compared to the replicate sections, which were hybridized with the respective sense probe. Results were considered positive if staining was observed with the antisense probe and no staining or weak background with the sense probe.

The cellular localization of the hybridization signal for each of the study probes is summarized in Table 5. Hybridization for Zmax1 was primarily detected in areas of bone involved in remodeling, including the endosteum and trabecular bone within the metaphysis. Hybridization in selected bone lining cells of the periosteum and epiphysis were also observed. Positive signal was also noted in chondrocytes within the growth plate, particularly in the proliferating chondrocytes. See Figs. 10, 11 and 12 for representative photomicrographs of *in situ* hybridization results.

TABLE 5

Summary of Zmax1 *in situ* hybridization in rat tibia

PROBE	SITE	ISH SIGNAL
Hu Zmax1	Epiphysis	
	Osteoblasts	+
	Osteoclasts	–
	Growth Plate	
	resting chondrocytes	-
	proliferating chondrocytes	+
	hypertrophic chondrocytes	-
	Metaphysis	
	osteoblasts	+
	osteoclasts	+

PROBE	SITE	ISH SIGNAL
	Diaphysis	-
	Endosteum	
	osteoblasts	+
	osteoclasts	+
	Periosteum	-
MsZmax1	Epiphysis	
	Osteoblasts	+
	Osteoclasts	-
	Growth Plate	
	resting chondrocytes	-
	proliferating chondrocytes	+
	hypertrophic chondrocytes	+
	Metaphysis	
	osteoblasts	+
	osteoclasts	+
	Diaphysis	-
	Endosteum	
	osteoblasts	+
	osteoclasts	+
	Periosteum	+

Legend: "+" = hybridization signal detected "-" = no hybridization signal detected
"ISH" – *In situ* hybridization

These studies confirm the positional expression of Zmax1 in cells involved in bone remodeling and bone formation. Zmax1 expression in the zone of proliferation and in the osteoblasts and osteoclasts of the proximal metaphysis, suggests that the Zmax1 gene is involved in the process of bone growth and mineralization. The activity and differentiation of osteoblasts and osteoclasts are closely coordinated during development as bone is formed and during growth as well as in adult life as bone undergoes continuous remodeling. The formation of internal bone structures and bone remodeling result from the coupling of bone resorption by activated osteoclasts with subsequent deposition of new material by osteoblasts. Zmax1 is related to the LDL receptor gene, and thus may be a receptor involved in mechanosensation and subsequent signaling in the process of bone

remodeling. Therefore, changes in the level of expression of this gene could impact on the rate of remodeling and degree of mineralization of bone.

XIV. Antisense

Antisense oligonucleotides are short synthetic nucleic acids that contain complementary base sequences to a targeted RNA. Hybridization of the RNA in living cells with the antisense oligonucleotide interferes with RNA function and ultimately blocks protein expression. Therefore, any gene for which the partial sequence is known can be targeted by an antisense oligonucleotide.

Antisense technology is becoming a widely used research tool and will play an increasingly important role in the validation and elucidation of therapeutic targets identified by genomic sequencing efforts.

Antisense technology was developed to inhibit gene expression by utilizing an oligonucleotide complementary to the mRNA that encodes the target gene. There are several possible mechanisms for the inhibitory effects of antisense oligonucleotides. Among them, degradation of mRNA by RNase H is considered to be the major mechanism of inhibition of protein function. This technique was originally used to elucidate the function of a target gene, but may also have therapeutic applications, provided it is designed carefully and properly.

An example of materials and methods for preparing antisense oligonucleotides can be performed as follows. Preliminary studies have been undertaken in collaboration with Sequiter (Natick, MA) using the antisense technology in the osteoblast-like murine cell line, MC3T3. These cells can be triggered to develop along the bone differentiation sequence. An initial proliferation period is characterized by minimal expression of differentiation markers and initial synthesis of collagenous extracellular matrix. Collagen matrix synthesis is required for subsequent induction of differentiation markers. Once the matrix synthesis begins, osteoblast marker genes are activated in a clear temporal sequence: alkaline phosphatase is induced at early times while bone sialoprotien and osteocalcin appear later in the differentiation process. This temporal sequence of gene expression is useful in monitoring the maturation and mineralization process. Matrix mineralization, which does not begin until several days after maturation has started,

involves deposition of mineral on and within collagen fibrils deep within the matrix near the cell layer-culture plate interface. The collagen fibril–associated mineral formed by cultured osteoblasts resembles that found in woven bone in vivo and therefore is used frequently as a study reagent.

MC3T3 cells were transfected with antisense oligonucleotides for the first week of the differentiation, according to the manufacturer's specifications (U.S. Patent No. 5,849,902).

The oligonucleotides designed for Zmax1 are given below:

10875: AGUACAGCUUCUUGCCAACCCAGUC

10876: UCCUCCAGGUCGAUGGUCAGCCCAU

10877: GUCUGAGUCCGAGUUCAAAUCCAGG

Fig. 13 shows the results of antisense inhibition of Zmax1 in MC3T3 cells. The three oligonucleotides shown above were transfected into MC3T3 and RNA was isolated according to standard procedures. Northern analysis clearly shows markedly lower steady state levels of the Zmax1 transcript while the control gene GAPDH remained unchanged. Thus, antisense technology using the primers described above allows for the study of the role of Zmax1 expression on bone biology.

XV. Yeast Two Hybrid

In order to identify the signaling pathway that Zmax1 participates in to modulate bone density, the yeast two hybrid protein interaction technology was utilized. This technique facilitates the identification of proteins that interact with one another by coupling tester proteins to components of a yeast transcription system (Fields and Song, 1989, *Nature* 340: 245-246; U.S. Pat. No. 5,283,173 by Fields and Song; Johnston, 1987, *Microbiol. Rev.* 51: 458-476; Keegan et al, 1986, *Science* 231: 699-704; Durfee et al, 1993, *Genes Dev.* 7: 555-569; Chien et al, 1991, *Proc. Natl. Acad. Sci USA* 88: 9578-9582; Fields et al., 1994, *Trends in Genetics* 10: 286-292; and Gyuris et al., 1993, *Cell* 75: 791-803). First a "bait" protein, the protein for which one seeks interacting proteins, is fused to the DNA binding domain of a yeast transcription factor. Second, a cDNA library is constructed that contains cDNAs fused to the transcriptional activation domain of the same yeast

transcription factor; this is termed the prey library. The bait construct and prey library are transformed into yeast cells and then mated to produce diploid cells. If the bait interacts with a specific prey from the cDNA library, the activation domain is brought into the vicinity of the promoter via this interaction. Transcription is then driven through selectable marker genes and growth on selective media indicates the presence of interacting proteins.

The amino acid sequence used in the yeast two hybrid experiments discussed herein consisted of the entire cytoplasmic domain and a portion of the transmembrane domain and is shown below (amino to carboxy orientation):

RVVCQRYAGA NGPFPHEYVS GTPHVPLNFI APGGSQHGPF TGIACGKSMM
SSVSLMGGRG GVPLYDRNHV TGASSSSSSS TKATLYPPIL NPPPSPATDP
SLYNMDMFYS SNIPATVRPY RPYIIRGMAP PTTPCSTDVC DSDYSASRWK
ASKYYLDLNS DSDPYPPPPT PHSQYLSAED SCPPSPATER SYFHLFPPPP
SPCTDSS

The last 6 amino acids of the putative transmembrane domain are indicated in bold. Putative SH3 domains are underlined. Additional amino acid sequences of 50 amino acids or greater in either the proteins encoded by the Zmax1 or HBM alleles can also be used as bait. The upper size of the polypeptide used as bait is limited only by the presence of a complete transmembrane domain (see Fig. 4), which will render the bait to be nonfunctional in a yeast two hybrid system. These additional bait proteins can be used to identify additional proteins which interact with the proteins encoded by HBM or Zmax1 in the focal adhesion signaling pathway or in other pathways in which these HBM or Zmax1 proteins may act. Once identified, methods of identifying agents which regulate the proteins in the focal adhesion signaling pathway or other pathways in which HBM acts can be performed as described herein for the HBM and Zmax1 proteins.

In order to identify cytoplasmic Zmax1 signaling pathways, the cytoplasmic domain of Zmax1 was subcloned into two bait vectors. The first vector was pDBleu, which was used to screen a brain, and Hela prey cDNA library cloned into the vector pPC86 (Clontech). The second bait vector used was pDBtrp, which was used to screen a cDNA prey library derived from the TE85 osteosarcoma cell line in

vector pOP46. Standard techniques known to those skilled in the art were used as described in Fields and Song, 1989, *Nature* 340: 245-246; U.S. Pat. No. 5,283,173 by Fields and Song; Johnston, 1987, *Microbiol. Rev.* 51: 458-476; Keegan et al., 1986, *Science* 231: 699-704; Durfee et al., 1993, *Genes Dev.* 7: 555-569; Chien et al., 1991, *Proc. Natl. Acad. Sci USA* 88: 9578-9582; Fields et al., 1994, *Trends in Genetics* 10: 286-292; and Gyuris et al., 1993, *Cell* 75: 791-803. The bait construct and prey cDNA libraries were transformed into yeast using standard procedures.

To perform the protein interaction screen, an overnight culture of the bait yeast strain was grown in 20 ml SD selective medium with 2% glucose (pDBLeu, SD -Leu medium, pDBtrp, SD –trp medium). The cultures were shaken vigorously at 30°C overnight. The cultures were diluted 1 : 10 with complete medium (YEPD with 2% glucose) and the cultures then incubated with shaking for 2 hrs at 30°C.

The frozen prey library was thawed, and the yeast cells reactivated by growing them in 150 ml YEPD medium with 2% glucose for 2 hrs at 30°C. A filter unit was sterilized with 70% ethanol and washed with sterile water to remove the ethanol. The cell densities of both bait and prey cultures were measured by determining the OD at 600 nm. An appropriate volume of yeast cells that corresponded to a cell number of 1 ml of OD 600 = 4 of each yeast strain, bait and prey (library) was placed in a 50 ml Falcon tube. The mixture was then filtered through the sterilized filter unit. The filter was then transferred onto a prewarmed YEPD agar plate with the cell side up, removing all air bubbles underneath the filter. Plates were then incubated at 30°C for 6 hrs. One filter was transferred into a 50 ml Falcon tube, and 10 ml of SD with 2% Glucose was added; cells were resuspended by vortexing for 10 sec.

The number of primary diploid cells (growth on SD -Leu, -Trp plates) versus the numbers of colony forming units growing on SD -Trp and SD -Leu plates only was then titered. Different dilutions were plated and incubated at 30ºC for two days. The number of colony forming units was then counted. The number of diploid colonies (colonies on SD -Leu -Trp plates) permits the calculation of whether or not the whole library of prey constructs was mated to the yeast expressing the bait. This information is important to judge the quality of the screen.

A. Indirect selection

Resuspended cells from 5 filtermatings were then pooled and the cells sedimented by centrifugation in a 50 ml Falcon tube. Cells were then resuspended in 16 ml SD medium with 2% Glc. Two ml of this cell suspension was plated onto 8 square plates each (SD -Leu, -Trp) with sterile glass beads and selected for diploid cells by incubating at 30°C for 18 - 20 hrs.

Cells were then scraped off the square plates, the cells centrifuged and combined into one 50 ml Falcon tube. The cell pellet was then resuspended in 25 ml of SD medium with 2% glucose. The cell number was then determined by counting of an appropriate dilution (usually 1:100 to 1:1000) with a Neugebauer chamber. Approximately 5 x 10^7 diploid cells were plated onto the selective medium. The observations about the growth of the bait strain together with irrelevant prey vectors helps to determine which selective plates will have to be chosen for the library screen. Generally, all screens were plated on one square plate each with SD -Leu, -Trp, -His; SD -Leu, -Trp, His, 5 mM 3AT, and SD -Leu, -Trp, -His, -Ade is recommended.

The yeast cells were then spread homogeneously with sterile glass beads and incubated at 30°C for 4 days. The number of colony forming yeast cells was titered by plating different dilutions of the scraped cell suspension onto SD -Leu, -Trp plates. Usually, plating of 100 µl of a 10^{-3} and 10^{-4} dilution gave 100 - 1000 colonies per plate.

B. Direct selection

Five filters with the mated yeast cells were each transferred into separate 50 ml Falcon tubes and the cells resuspended with 10 ml SD medium with 2% Glc, each, followed by vortexing for 10 sec. The resuspended cells were combined and centrifuged in a Beckman centrifuge at 3000 rpm. The supernatant was discarded and the cells resuspended in 6 ml of SD medium with 2% Glc. Two ml of the suspension was spread onto each selective square plate and incubated at 30°C for 4 - 5 days.

C. Isolation of Single Colonies

Yeast cells from an isolated colony were picked with a sterile tooth pick and transferred into individual wells of a 96 well plate. The cells were resuspended in 50 µl of SD -Leu, -Trp, -His medium and incubated at 30°C for one day. The yeast cells were then stamped onto a SD -Leu, -Trp, -His plate in 96 well format and incubated at 30°C for 2 days. Yeast cells were also stamped onto a Nylon filter covering a YEPD plate and incubated at 30°C for one day. The cells on the Nylon filter were used for the analysis of the ß - Gal reporter activity.

Yeast colonies were scraped from the SD -Leu, -Trp, -His plate with a sterile tooth pick, and reconfigured, if necessary, according to the ß - Gal activity and then resuspended in 20 % glycerol. This served as a master plate for storage at -80°C.

For DNA preparation, yeast cells from the glycerol stock were stamped onto a SD -Trp plate and incubated at 30°C for 2 days. After two days of incubation, the yeast colonies were ready for colony PCR and sequencing. Standard colony PCR conditions were used to amplify inserts from preys recovered from the interaction screen. Sequencing was done using standard sequencing reactions and ABI377 (Perkin Elmer) fluorescent sequencing machines.

D. Verification of bait/prey interaction

Glycerol stocks of the prey of interest were thawed and inoculated in a 10 ml overnight culture of SD with glucose -Trp. After overnight growth, plasmid DNA preparation was performed using the BIO 101 RPM Yeast Plasmid Isolation Kit with 10 ml of culture. The culture was centrifuged and transfered to a 1.5 ml microcentrifuge tube. Yeast Lysis Matrix was then added to the pellet followed by 250 µl of Alkaline Lysis Solution. Samples were then vortexed for 5 minutes. 250 µl Neutralizing Solution was added and the sample mixed briefly. Samples were centrifuged for 2 minutes at room temperature in a microcentrifuge. The supernatant was transferred to a Spin Filter avoiding debris and Lysis Matrix. 250 µl of Glassmilk Spin Buffer was added, and the tubes inverted to mix. Samples were centrifuged for 1 min and the liquid in the Catch Tube was discarded. 500 µl of Wash Solution was added, the samples were centrifuged for 1 min, and the wash solution was discarded. The wash step was repeated once followed by a 1 min dry

centrifugation to drive the remaining liquid out of the Spin Filter. The filter was transferred to a new Catch Tube and 100 µl of sterile H_2O was added; samples were then vortexed briefly to resuspend and centrifuged for 30 seconds to collect the DNA in the bottom of the Catch Tube.

Five µl of DNA was then transformed into DH10B Electromax cells using standard procedures and glycerol stocks prepared. Miniprep DNA was prepared using the Qiagen QIAprep Spin Miniprep Kit. DNA was finally eluted with 30 µl of Qiagen EB buffer. One µl of the plasmid DNA samples was then used to transform yeast cells using standard procedures. After 2 days of growth on SD –trp media, colonies were picked and patched onto fresh media. Similarly, bait colonies were patched onto SD –Leu media. Both were grown overnight at 30°C.

For mating, cells from bait and prey patches were spread together on YAPD media and incubated at 30°C for 12 hr. This plate was then replicaplated onto an SD Agar-Leu-Trp plate and grown for 2 days at 30°C. To test the strength of interaction these plates were replicaplated onto SD Agar-Leu-Trp-His, SD Agar-Leu-Trp-His with 5 mM 3AT and 10 mM 3AT, SD Agar-Leu-Trp-His-Ade, and SD Agar-Leu-Trp-Ura media and grown for 2 days at 30°C.

E. Galacton Star β-Galactosidase Activity Assay

After streaking and replica plating positive interactors on selection plates, colonies were placed in a 96 well dish with 200 µl of SD-medium, leaving wells 1 and 96 blank. Ten microliters from the first 96 well dish was plated into another flat bottom 96 well dish containing 100 µl of SD-medium. Controls consisted of a negative control and a very weak positive control. The cell density was measured at OD_{600} (a value of 1 corresponds to 1×10^7 cells utilizing a 96 well spectrophotometer). The OD was usually between 0.03 and 0.10. Using microplates specifically for the luminometer, 50 µl of reaction mixture were pipetted into each well. Fifty microliters of culture were then added and mixed by pipetting up and down twice. The reaction was incubated for 30 minutes at room temperature followed by measurement of Relative Light Units using a luminometer.

Table 6 lists the genes identified in the yeast two hybrid screens from the 3 prey libraries tested. Two genes, zyxin and axin, were found to interact with the

cytoplasmic domain of Zmax1 in all three screens. Three genes, alpha-actinin, TCB and S1-5 interacted in two of the three screens.

A variety of proteins found at sites of cell-cell and cell-matrix contact (focal contacts/adesion plaques) were shown to interact with the cytoplasmic domain of Zmax1. These include alpha-actinin, Trio, Pinch-like protein, and Zyxin. PINCH is a LIM domain-containing protein that is known to interact with integrin-linked kinase, an early signaler in integrin and growth factor signaling pathways. The finding of a closely related gene in the yeast two hybrid screen raises the possibility of a novel pathway linked to integrin signaling from extracellular matrix signals. Trio, also known to localize to focal adhesions, is thought to play a key role in coordinating cell-matrix interactions and cytoskeletal rearrangements involved in cell movement. Zyxin, another LIM domain-containing protein, is also localized to adhesion plaques and is thought to be involved in reorganization of the cytoskeleton when triggers are transmitted via integrin signaling pathways. Zyxin also interacts with alpha actinin, which we identified as interacting with Zmax1. Other LIM domain containing proteins identified include the human homologue of mouse ajuba, LIMD1, and a novel LIMD1-like protein.

Axin was also identified from the two hybrid experiments. This protein is involved in inhibition of the Wnt signaling pathway and interacts with the tumor suppressor APC. There is a link here with the focal adhesion signaling described above: one common step in the two pathways involves inhibition of glycogen synthase kinase 3, which in turn results in the activation of ß-catenin/Lef-1 and AP-1 transcription factors. Axin/APC are involved in this as well as integrin linked kinase. The Wnt pathway has a role in determining cell fates during embryogenesis. If inappropriately activated, the Wnt pathway may also lead to cancer. The Wnt pathway also seems to have a role in cytoskeletal rearrangements. A model depicting Zmax1 involvement in focal adhesion signaling is depicted in Fig. 15.

This data coupled with other studies suggest that integrin signaling pathways have a role in cellular responses to mechanical stress and adhesion. This provides an attractive model for the mechanism of action of Zmax1 in bone biology. It is possible that Zmax1 is involved in sensing either mechanical stress directly or

binding a molecule in the extracellular matrix that is related to mechanical sensation. Signaling through subsequent pathways may be involved in bone remodeling due to effects on cell morphology, cell adhesion, migration, proliferation, differentiation, and apoptosis in bone cells.

Table 6: Yeast Two Hybrid Results

Gene Symbol	Gene	Genbank Accession #	NT SEQ ID NO:	AA SEQ ID NO:
ACTN1	alpha-actinin	NM_001102	63	
AES	amino-terminal enhancer of	NM_001130.3	64	
AIP4	atrophin-1 interacting protein	AF038564.1	65	
Novel	Ajuba		66	
AXIN	Wnt signaling	AF009674.1	67	
CDC23	cell division cycle 23, yeast, homolog	NM_004661.1	68	
HSM800944	Similar to TRIO	AL117435.1	69	
HSM800936		AL117427.1	70	
Novel	Similar to LIM domains containing protein 1		71	
DEEPEST	mitotic spindle coiled-coil related protein	NM_006461.1	72	
ECM1	extracellular matrix protein 1	U65932.1	73	
EF1A	elongation factor 1-alpha	X16869.1	74	
FN	fibronectin	X02761.1	75	
HOXB13	homeodomain protein	U81599.1	76	
Novel	Glu-Lys Rich protein		77	
LIMD1	LIM domains containing 1	NM_014240.1	78	
Novel	PINCH-like		79	
RANBPM	centrosomal protein	NM_005493.1	80	
S1-5	extracellular protein	U03877.1	81	
TCB	gene encoding cytosolic thyroid hormone-binding	M26252.1	82	
TID	tumorous imaginal discs	NM_005147.1	83	
ZYX	Zyxin	NM_003461.1	84	
TRIO	GTPase	U42390.1	85	
HUMPITPB	phosphatidylinositol transfer protein	D30037.1	86	
ACTN1	alpha-actinin	NP_001093.1		87

Gene Symbol	Gene	Genbank Accession #	NT SEQ ID NO:	AA SEQ ID NO:
AES	amino-terminal enhancer of	NP_001121.2		88
AIP4	atrophin-1 interacting protein	AAC04845.1		89
Novel	Ajuba			90
AXIN	Wnt signalling	AAC51624.1		91
CDC23	cell division cycle 23, yeast homolog	NP_004652.1		92
Novel	Similar to TRIO CAB55923.1			93
Novel	Similar to LIM domains containing protein 1			94
DEEPEST	mitotic spindle coiled-coil related protein	NP_006452.1		95
ECM1	extracellular matrix protein 1	AAB05933.1		96
EF1A	elongation factor 1-alpha	CAA34756.1		97
FN	fibronectin	CAA26536.1		98
Novel	Glu-Lys rich protein			99
HOXB13	homeodomain protein B13	AAB39863.1		100
LIMD1	LIM domains containing 1	NP_055055.1		101
Novel	PINCH-like			102
RANBPM	centrosomal protein	NP_005484.1		103
S1-5	extracellular protein	AAA65590.1		104
TCB	cytosolic thyroid hormone-binding protein	AAA36672.1		105
TID	tumorous imaginal discs	NP_005138.1		106
ZYX	Zyxin	NP_003452.1		107
TRIO	GTPase	AAC34245.1		108
PTDINSTP	phosphatidylinositol transfer protein beta isoform	P48739		109

In light of the model depicted in Fig. 15 and the results shown in Table 6, another aspect contemplated by the invention would be to regulate bone density and bone mass disorders by the regulating focal adhesion signaling. The regulation can occur by regulating the DNA, mRNA transcript or protein encoded by any of the members involved in the focal adhesion signaling pathway as identified by the yeast two hybrid system.

Also contemplated are the novel nucleic acids and proteins identified by the HBM yeast two hybrid system. These include but are not limited to SEQ ID NO: 66

(Ajuba), SEQ ID NO: 71 (a gene similar to a gene encoding LIM domains containing protein 1), SEQ ID NO: 77 (Glu-Lys Rich protein), SEQ ID NO: 79 (PINCH-like gene), SEQ ID NO: 90 (Ajuba protein), SEQ ID NO: 93 (protein similar to TRIO), SEQ ID NO: 94 (), SEQ ID NO: 99 (Glu-Lys rich protein) and SEQ ID NO: 102 (PINCH-like protein).

XVI. Potential Function

The protein encoded by Zmax1 is related to the Low Density Lipoprotein receptor (LDL receptor). *See*, Goldstein et al, *Ann. Rev. Cell Biology*, 1:1-39 (1985); Brown et al, *Science*, 232:34-47 (1986). The LDL receptor is responsible for uptake of low density lipoprotein, a lipid-protein aggregate that includes cholesterol. Individuals with a defect in the LDL receptor are deficient in cholesterol removal and tend to develop artherosclerosis. In addition, cells with a defective LDL receptor show increased production of cholesterol, in part because of altered feedback regulation of cholesterol synthetic enzymes and in part because of increased transcription of the genes for these enzymes. In some cell types, cholesterol is a precursor for the formation of steroid hormones.

Thus, the LDL receptor may, directly or indirectly, function as a signal transduction protein and may regulate gene expression. Because Zmax1 is related to the LDL receptor, this protein may also be involved in signaling between cells in a way that affects bone remodeling.

The glycine 171 amino acid is likely to be important for the function of Zmax1 because this amino acid is also found in the mouse homologue of Zmax1. The closely related LRP6 protein also contains glycine at the corresponding position (Brown et al, *Biochemical and Biophysical Research Comm.*, 248:879-888 (1988)). Amino acids that are important in a protein's structure or function tend to be conserved between species, because natural selection prevents mutations with altered amino acids at important positions from arising.

In addition, the extracellular domain of Zmax1 contains four repeats consisting of five YWTD motifs followed by an EFG motif. This 5YWTD+EGF repeat is likely to form a distinct folded protein domain, as this repeat is also found in the LDL receptor and other LDL receptor-related proteins. The first three

5YWTD+EGF repeats are very similar in their structure, while the fourth is highly divergent. Glycine 171 occurs in the central YWTD motif of the first 5YWTD+EGF repeat in Zmax1. The other two similar 5YWTD+EGF repeats of Zmax1 also contain glycine at the corresponding position, as does the 5YWTD+EGF repeat in the LDL receptor protein. However, only 17.6% of the amino acids are identical among the first three 5YWTD+EGF repeats in Zmax1 and the single repeat in the LDL receptor. These observations indicate that glycine 171 is essential to the function of this repeat, and mutation of glycine 171 causes a functional alteration of Zmax1. The cDNA and peptide sequences are shown in Figs. 6A-6E. The critical base at nucleotide position 582 is indicated in bold and is underlined.

Northern blot analysis (Figs. 7A-B) reveals that Zmax1 is expressed in human bone tissue as well as numerous other tissues. A multiple-tissue Northern blot (Clontech, Palo Alto, CA) was probed with exons from Zmax1. As shown in Fig. 7A, the 5.5 kb Zmax1 transcript was highly expressed in heart, kidney, lung, liver and pancreas and is expressed at lower levels in skeletal muscle and brain. A second northern blot, shown in Fig. 7B, confirmed the transcript size at 5.5 kb, and indicated that Zmax1 is expressed in bone, bone marrow, calvaria and human osteoblastic cell lines.

Taken together, these results coupled with the yeast two hybrid results indicate that the HBM polymorphism in the Zmax1 gene is responsible for the HBM phenotype, and that the Zmax1 gene is important in bone development. In addition, because mutation of Zmax1 can alter bone mineralization and development, it is likely that molecules that bind to Zmax1 may usefully alter bone development. Such molecules may include, for example, small molecules, proteins, RNA aptamers, peptide aptamers, and the like.

XVII. Preparation of Nucleic Acids, Vectors, Transformations and Host Cells

Large amounts of the nucleic acids of the present invention may be produced by replication in a suitable host cell. Natural or synthetic nucleic acid fragments coding for a desired fragment will be incorporated into recombinant nucleic acid constructs, usually DNA constructs, capable of introduction into and replication in a

prokaryotic or eukaryotic cell. Usually the nucleic acid constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to (with and without integration within the genome) cultured mammalian or plant or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention is described, for example, in Sambrook et al, *Molecular Cloning. A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989) or Ausubel et al, *Current Protocols in Molecular Biology*, J. Wiley and Sons, NY (1992).

The nucleic acids of the present invention may also be produced by chemical synthesis, e.g., by the phosphoramidite method described by Beaucage et al, *Tetra. Letts.*, 22:1859-1862 (1981) or the triester method according to Matteucci,et al, J. *Am. Chem. Soc.*, 103:3185 (1981), and may be performed on commercial, automated oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Nucleic acid constructs prepared for introduction into a prokaryotic or eukaryotic host may comprise a replication system recognized by the host, including the intended nucleic acid fragment encoding the desired protein, and will preferably also include transcription and translational initiation regulatory sequences operably linked to the protein encoding segment. Expression vectors may include, for example, an origin of replication or autonomously replicating sequence (ARS) and expression control sequences, a promoter, an enhancer and necessary processing information sites, such as ribosome-binding sites, RNA splice sites, polyadenylation sites, transcriptional terminator sequences, and mRNA stabilizing sequences. Secretion signals may also be included where appropriate, whether from a native HBM or Zmax1 protein or from other receptors or from secreted proteins of the same or related species, which allow the protein to cross and/or lodge in cell membranes, and thus attain its functional topology, or be secreted from the cell. Such vectors may be prepared by means of standard recombinant techniques well

known in the art and discussed, for example, in Sambrook et al, *Molecular Cloning. A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989) or Ausubel et al, *Current Protocols in Molecular Biology*, J. Wiley and Sons, NY (1992).

An appropriate promoter and other necessary vector sequences will be selected so as to be functional in the host, and may include, when appropriate, those naturally associated with Zmax1 or HBM genes. Examples of workable combinations of cell lines and expression vectors are described in Sambrook et al, *Molecular Cloning. A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989) or Ausubel et al, *Current Protocols in Molecular Biology*, J. Wiley and Sons, NY (1992). Many useful vectors are known in the art and may be obtained from such vendors as Stratagene, New England BioLabs, Promega Biotech, and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization, and others. Vectors and promoters suitable for use in yeast expression are further described in EP 73,675A. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers et al, *Nature*, 273:113 (1978)) or promoters derived from murine Moloney leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. In addition, the construct may be joined to an amplifiable gene (e.g., DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1983).

While such expression vectors may replicate autonomously, they may also replicate by being inserted into the genome of the host cell, by methods well known in the art.

Expression and cloning vectors will likely contain a selectable marker, a gene encoding a protein necessary for survival or growth of a host cell transformed with the vector. The presence of this gene ensures growth of only those host cells which express the inserts. Typical selection genes encode proteins that a) confer resistance to antibiotics or other toxic substances, e.g. ampicillin, neomycin, methotrexate, etc.; b) complement auxotrophic deficiencies, or c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli. The choice of the proper selectable marker will depend on the host cell, and appropriate markers for different hosts are well known in the art.

The vectors containing the nucleic acids of interest can be transcribed *in vitro*, and the resulting RNA introduced into the host cell by well-known methods, e.g., by injection (see, Kubo et al, *FEBS Letts*. 241:119 (1988)), or the vectors can be introduced directly into host cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook et al., 1989 and Ausubel et al., 1992. The introduction of the nucleic acids into the host cell by any method known in the art, including those described above, will be referred to herein as "transformation." The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and proteins of the present invention may be prepared by expressing the Zmax1 or HBM nucleic acids or portions thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *Escherichia coli*, although other prokaryotes, such as *Bacillus subtilis* or *Pseudomonas* may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect, or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian

cells in culture is per se well known. See, Jakoby and Pastan (eds.), *Cell Culture. Methods in Enzymology*, volume 58, Academic Press, Inc., Harcourt Brace Jovanovich, NY, (1979)). Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK, and COS cell lines, although it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g., to provide higher expression desirable glycosylation patterns, or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g., by resistance to ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the nucleic acids of the present invention will be useful not only for the production of the nucleic acids and proteins of the present invention, but also, for example, in studying the characteristics of Zmax1 or HBM proteins.

Antisense nucleic acid sequences arc useful in preventing or diminishing the expression of Zmax1 or HBM, as will be appreciated by one skilled in the art. For example, nucleic acid vectors containing all or a portion of the Zmax1 or HBM gene or other sequences from the Zmax1 or HBM region may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with Zmax1 or HBM transcription and/or translation and/or replication.

The probes and primers based on the Zmax1 and HBM gene sequences disclosed herein are used to identify homologous Zmax1 and HBM gene sequences and proteins in other species. These Zmax1 and HBM gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated.

XVIII. Protein Expression and Purification

Expression and purification of the HBM protein of the invention can be performed essentially as outlined below. To facilitate the cloning, expression and purification of membrane and secreted protein from the HBM gene, a gene expression system, such as the pET System (Novagen), for cloning and expression of recombinant proteins in *E. coli* was selected. Also, a DNA sequence encoding a peptide tag, the His-Tap, was fused to the 3' end of DNA sequences of interest to facilitate purification of the recombinant protein products. The 3' end was selected for fusion to avoid alteration of any 5' terminal signal sequence.

Nucleic acids chosen, for example, from the nucleic acids set forth in SEQ ID NOS: 1, 3 and 5-12 for cloning HBM were prepared by polymerase chain reaction (PCR). Synthetic oligonucleotide primers specific for the 5' and 3' ends of the HBM nucleotide sequence were designed and purchased from Life Technologies (Gaithersburg, MD). All forward primers (specific for the 5' end of the sequence) were designed to include an NcoI cloning site at the 5' terminus. These primers were designed to permit initiation of protein translation at the methionine residue encoded within the NcoI site followed by a valine residue and the protein encoded by the HBM DNA sequence. All reverse primers (specific for the 3' end of the sequence) included an EcoRI site at the 5' terminus to permit cloning of the HBM sequence into the reading frame of the pET-28b. The pET-28b vector provided a sequence encoding an additional 20 carboxyl-terminal amino acids including six histidine residues (at the C-terminus), which comprised the histidine affinity tag.

Genomic DNA prepared from the HBM gene was used as the source of template DNA for PCR amplification (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1994)). To amplify a DNA sequence containing the HBM nucleotide sequence, genomic DNA (50 ng) was introduced into a reaction vial containing 2 mM $MgCl_2$, 1 μM synthetic oligonucleotide primers (forward and reverse primers) complementary to and flanking a defined HBM, 0.2 mM of each of deoxynucleotide triphosphate, dATP, dGTP, dCTP, dTTP and 2.5 units of heat stable DNA polymerase (Amplitaq, Roche Molecular Systems, Inc., Branchburg, NJ) in a final volume of 100 microliters.

Upon completion of thermal cycling reactions, each sample of amplified DNA was purified using the Qiaquick Spin PCR purification kit (Qiagen, Gaithersburg, MD). All amplified DNA samples were subjected to digestion with the restriction endonucleases, e.g., NcoI and EcoRI (New England BioLabs, Beverly, MA) (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)). DNA samples were then subjected to electrophoresis on 1.0% NuSeive (FMC BioProducts, Rockland, ME) agarose gels. DNA was visualized by exposure to ethidium bromide and long wave UV irradiation. DNA contained in slices isolated from the agarose gel was purified using the Bio 101 GeneClean Kit protocol (Bio 101, Vista, CA).

The pET-28b vector was prepared for cloning by digestion with restriction endonucleases, e.g., NcoI and EcoRI (New England BioLabs, Beverly, MA) (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)). The pET-28a vector, which encodes the histidine affinity tag that can be fused to the 5' end of an inserted gene, was prepared by digestion with appropriate restriction endonucleases.

Following digestion, DNA inserts were cloned (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)) into the previously digested pET-28b expression vector. Products of the ligation reaction were then used to transform the BL21 strain of *E. coli* (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)) as described below.

Competent bacteria, *E. coli* strain BL21 or *E. coli* strain BL21 (DE3), were transformed with recombinant pET expression plasmids carrying the cloned HBM sequence according to standard methods (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)). Briefly, 1 μl of ligation reaction was mixed with 50 μl of electrocompetent cells and subjected to a high voltage pulse, after which samples were incubated in 0.45 ml SOC medium (0.5% yeast extract, 2.0% tryptone, 10 mM NaCl, 2.5 mM KCl, 10 mM $MgCl_2$, 10 mM $MgSO_4$ and 20 mM glucose) at 37°C with shaking for 1 hour. Samples were then spread on LB agar plates containing 25 μg/ml kanamycin sulfate for growth

overnight. Transformed colonies of BL21 were then picked and analyzed to evaluate cloned inserts, as described below.

Individual BL21 clones transformed with recombinant pET-28b HBM nucleotide sequences were analyzed by PCR amplification of the cloned inserts using the same forward and reverse primers specific for the HBM sequences that were used in the original PCR amplification cloning reactions. Successful amplification verifies the integration of the HBM sequence in the expression vector (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994)).

Individual clones of recombinant pET-28b vectors carrying properly cloned HBM nucleotide sequences were picked and incubated in 5 ml of LB broth plus 25 μg/ml kanamycin sulfate overnight. The following day plasmid DNA was isolated and purified using the Qiagen plasmid purification protocol (Qiagen Inc., Chatsworth, CA).

The pET vector can be propagated in any *E. coli* K-12 strain, e.g., HMS174, HB101, JM109, DH5 and the like, for purposes of cloning or plasmid preparation. Hosts for expression include *E. coli* strains containing a chromosomal copy of the gene for T7 RNA polymerase. These hosts were lysogens of bacteriophage DE3, a lambda derivative that carries the lacI gene, the lacUV5 promoter and the gene for T7 RNA polymerase. T7 RNA polymerase was induced by addition of isopropyl-β-D-thiogalactoside (IPTG), and the T7 RNA polymerase transcribes any target plasmid containing a functional T7 promoter, such as pET-28b, carrying its gene of interest. Strains include, for example, BL21(DE3) (Studier et al, *Meth. Enzymol.*, 185:60-89 (1990)).

To express the recombinant HBM sequence, 50 ng of plasmid DNA are isolated as described above to transform competent BL21(DE3) bacteria as described above (provided by Novagen as part of the pET expression kit). The lacZ gene (β-galactosidase) is expressed in the pET-System as described for the HBM recombinant constructions. Transformed cells were cultured in SOC medium for 1 hour, and the culture was then plated on LB plates containing 25 μg/ml kanamycin sulfate. The following day, the bacterial colonies were pooled and grown in LB

medium containing kanamycin sulfate (25 μg/ml) to an optical density at 600 nM of 0.5 to 1.0 O.D. units, at which point 1 mM IPTG was added to the culture for 3 hours to induce gene expression of the HBM recombinant DNA constructions.

After induction of gene expression with IPTG, bacteria were collected by centrifugation in a Sorvall RC-3B centrifuge at 3500 x g for 15 minutes at 4°C. Pellets were resuspended in 50 ml of cold mM Tris-HCl, pH 8.0, 0.1 M NaCl and 0.1 mM EDTA (STE buffer). Cells were then centrifuged at 2000 x g for 20 minutes at 4°C. Wet pellets were weighed and frozen at -80°C until ready for protein purification.

A variety of methodologies known in the art can be used to purify the isolated proteins (Coligan et al, *Current Protocols in Protein Science,* John Wiley & Sons (1995)). For example, the frozen cells can be thawed, resuspended in buffer and ruptured by several passages through a small volume microfluidizer (Model M-110S, Microfluidics International Corp., Newton, MA). The resultant homogenate is centrifuged to yield a clear supernatant (crude extract) and, following filtration, the crude extract is fractioned over columns. Fractions are monitored by absorbance at OD_{280} nm and peak fractions may be analyzed by SDS-PAGE.

The concentrations of purified protein preparations are quantified spectrophotometrically using absorbance coefficients calculated from amino acid content (Perkins, *Eur. J. Biochem.*, 157:169-180 (1986)). Protein concentrations are also measured by the method of Bradford, *Anal. Biochem.*, 72:248-254 (1976) and Lowry et al, *J. Biol. Chem.*, 193:265-275 (1951) using bovine serum albumin as a standard.

SDS-polyacrylamide gels of various concentrations were purchased from BioRad (Hercules, CA), and stained with Coomassie blue. Molecular weight markers may include rabbit skeletal muscle myosin (200 kDa), *E. coli* β-galactosidase (116 kDa), rabbit muscle phosphorylase B (97.4 kDa), bovine serum albumin (66.2 kDa), ovalbumin (45 kDa), bovine carbonic anyhdrase (31 kDa), soybean trypsin inhibitor (21.5 kDa), egg white lysozyme (14.4 kDa) and bovine aprotinin (6.5 kDa).

Once a sufficient quantity of the desired protein has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by *in vitro* or *in vivo* techniques well known in the art. Monoclonal antibodies to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas (Kohler, *Nature*, 256:495 (1975)). In summary, a mouse is inoculated with a few micrograms of HBM protein over a period of two weeks. The mouse is then sacrificed. The cells that produce antibodies are then removed from the mouse's spleen. The spleen cells are then fused with polyethylene glycol with mouse myeloma cells. The successfully fused cells are diluted in a microtiter plate and growth of the culture is continued. The amount of antibody per well is measured by immunoassay methods such as ELISA (Engvall, *Meth. Enzymol.*, 70:419 (1980)). Clones producing antibody can be expanded and further propagated to produce HBM antibodies. Other suitable techniques involve *in vitro* exposure of lymphocytes to the antigenic polypeptides, or alternatively, to selection of libraries of antibodies in phage or similar vectors. See Huse et al, *Science,* 246:1275-1281 (1989). For additional information on antibody production see Davis et al, *Basic Methods in Molecular Biology*, Elsevier, NY, Section 21-2 (1989).

XIX. Methods of Use: Gene Therapy

In recent years, significant technological advances have been made in the area of gene therapy for both genetic and acquired diseases. (Kay et al, *Proc. Natl. Acad. Sci. USA*, 94:12744-12746 (1997)) Gene therapy can be defined as the deliberate transfer of DNA for therapeutic purposes. Improvement in gene transfer methods has allowed for development of gene therapy protocols for the treatment of diverse types of diseases. Gene therapy has also taken advantage of recent advances in the identification of new therapeutic genes, improvement in both viral and nonviral gene delivery systems, better understanding of gene regulation, and improvement in cell isolation and transplantation.

The preceding experiments identify the HBM gene as a dominant mutation conferring elevated bone mass. The fact that this mutation is dominant indicates that

expression of the HBM protein causes elevated bone mass. Older individuals carrying the HBM gene, and, therefore expressing the HBM protein, do not suffer from osteoporosis. These individuals are equivalent to individuals being treated with the HBM protein. These observations are a strong experimental indication that therapeutic treatment with the HBM protein prevents osteoporosis. The bone mass elevating activity of the HBM gene is termed "HBM function."

Therefore, according to the present invention, a method is also provided of supplying HBM function to mesenchymal stem cells (Onyia et al, *J. Bone Miner. Res.*, 13:20-30 (1998); Ko et al, *Cancer Res.*, 56:4614-4619 (1996)). Supplying such a function provides protection against osteoporosis. The HBM gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. In such a situation, the gene will be expressed by the cell from the extrachromosomal location.

Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate co-precipitation, and viral transduction are known in the art, and the choice of method is within the competence of one skilled in the art (Robbins, Ed., *Gene Therapy Protocols*, Human Press, NJ (1997)). Cells transformed with the HBM gene can be used as model systems to study osteoporosis and drug treatments that promote bone growth.

As generally discussed above, the HBM gene or fragment, where applicable, may be used in gene therapy methods in order to increase the amount of the expression products of such genes in mesenchymal stem cells. It may be useful also to increase the level of expression of a given HBM protein, or a fragment thereof, even in those cells in which the wild type gene is expressed normally. Gene therapy would be carried out according to generally accepted methods as described by, for example, Friedman, *Therapy for Genetic Diseases*, Friedman, Ed., Oxford University Press, pages 105-121 (1991).

A virus or plasmid vector containing a copy of the HBM gene linked to expression control elements and capable of replicating inside mesenchymal stem

cells, is prepared. Suitable vectors are known and described, for example, in U.S. Patent No. 5,252,479 and WO 93/07282, the disclosures of which are incorporated by reference herein in their entirety. The vector is then injected into the patient, either locally into the bone marrow or systemically (in order to reach any mesenchymal stem cells located at other sites, i.e., in the blood). If the transfected gene is not permanently incorporated into the genome of each of the targeted cells, the treatment may have to be repeated periodically.

Gene transfer systems known in the art may be useful in the practice of the gene therapy methods of the present invention. These include viral and non-viral transfer methods. A number of viruses have been used as gene transfer vectors, including polyoma, i.e., SV40 (Madzak et al, *J. Gen. Virol.*, 73:1533-1536 (1992)), adenovirus (Berkner, *Curr. Top. Microbiol. Immunol.*, 158:39-61 (1992); Berkner et al, *Bio Techniques*, 6:616-629 (1988); Gorziglia et al, *J. Virol.*, 66:4407-4412 (1992); Quantin et al, *Proc. Natl. Acad. Sci. USA*, 89:2581-2584 (1992); Rosenfeld et al, *Cell*, 68:143-155 (1992); Wilkinson et al, *Nucl. Acids Res.*, 20:2233-2239 (1992); Stratford-Perricaudet et al, *Hum. Gene Ther.*, 1:241-256 (1990)), vaccinia virus (Mackett et al, *Biotechnology*, 24:495-499 (1992)), adeno-associated virus (Muzyczka, *Curr. Top. Microbiol. Immunol.*, 158:91-123 (1992); Ohi et al, *Gene*, 89:279-282 (1990)), herpes viruses including HSV and EBV (Margolskee, *Curr. Top. Microbiol. Immunol.*, 158:67-90 (1992); Johnson et al, *J. Virol.*, 66:2952-2965 (1992); Fink et al, *Hum. Gene Ther.*, 3:11-19 (1992); Breakfield et al, *Mol. Neurobiol.*, 1:337-371 (1987;) Fresse et al, *Biochem. Pharmacol.*, 40:2189-2199 (1990)), and retroviruses of avian (Brandyopadhyay et al, *Mol. Cell Biol.*, 4:749-754 (1984); Petropouplos et al, *J. Virol.*, 66:3391-3397 (1992)), murine (Miller, *Curr. Top. Microbiol. Immunol.*, 158:1-24 (1992); Miller et al, *Mol. Cell Biol.*, 5:431-437 (1985); Sorge et al, *Mol. Cell Biol.*, 4:1730-1737 (1984); Mann et al, *J. Virol.*, 54:401-407 (1985)), and human origin (Page et al, *J. Virol.*, 64:5370-5276 (1990); Buchschalcher et al, *J. Virol.*, 66:2731-2739 (1992)). Most human gene therapy protocols have been based on disabled murine retroviruses.

Non-viral gene transfer methods known in the art include chemical techniques such as calcium phosphate coprecipitation (Graham et al, *Virology*,

52:456-467 (1973); Pellicer et al, *Science*, 209:1414-1422 (1980)), mechanical techniques, for example microinjection (Anderson et al, *Proc. Natl. Acad. Sci. USA*, 77:5399-5403 (1980); Gordon et al, *Proc. Natl. Acad. Sci. USA*, 77:7380-7384 (1980); Brinster et al, *Cell*, 27:223-231 (1981); Constantini et al, *Nature*, 294:92-94 (1981)), membrane fusion-mediated transfer via liposomes (Felgner et al, *Proc. Natl. Acad. Sci. USA*, 84:7413-7417 (1987); Wang et al, *Biochemistry*, 28:9508-9514 (1989); Kaneda et al, *J. Biol. Chem.*, 264:12126-12129 (1989); Stewart et al, *Hum. Gene Ther.*, 3:267-275 (1992); Nabel et al, *Science*, 249:1285-1288 (1990); Lim et al, *Circulation*, 83:2007-2011 (1992)), and direct DNA uptake and receptor-mediated DNA transfer (Wolff et al, *Science*, 247:1465-1468 (1990); Wu et al, *BioTechniques*, 11:474-485 (1991); Zenke et al, *Proc. Natl. Acad. Sci. USA*, 87:3655-3659 (1990); Wu et al, *J. Biol. Chem.*, 264:16985-16987 (1989); Wolff et al, *BioTechniques*, 11:474-485 (1991); Wagner et al, 1990; Wagner et al, *Proc. Natl. Acad. Sci. USA*, 88:4255-4259 (1991); Cotten et al, *Proc. Natl. Acad. Sci. USA*, 87:4033-4037 (1990); Curiel et al, *Proc. Natl. Acad. Sci. USA*, 88:8850-8854 (1991); Curiel et al, *Hum. Gene Ther.*, 3:147-154 (1991)). Viral-mediated gene transfer can be combined with direct *in vivo* vectors to the mesenchymal stem cells and not into the surrounding cells (Romano et al, *In Vivo*, 12(1):59-67 (1998); Gonez et al, *Hum. Mol. Genetics*, 7(12):1913-9 (1998)). Alternatively, the retroviral vector producer cell line can be injected into the bone marrow (Culver et al, *Science*, 256:1550-1552 (1992)). Injection of producer cells would then provide a continuous source of vector particles. This technique has been approved for use in humans with inoperable brain tumors.

In an approach which combines biological and physical gene transfer methods, plasmid DNA of any size is combined with a polylysine-conjugated antibody specific to the adenovirus hexon protein, and the resulting complex is bound to an adenovirus vector. The trimolecular complex is then used to infect cells. The adenovirus vector permits efficient binding, internalization, and degradation of the endosome before the coupled DNA is damaged.

Liposome/DNA complexes have been shown to be capable of mediating direct *in vivo* gene transfer. While in standard liposome preparations the gene

transfer process is non-specific, localized *in vivo* uptake and expression have been reported in tumor deposits, for example, following direct *in situ* administration (Nabel, *Hum. Gene Ther.*, 3:399-410 (1992)).

XX. Methods of Use: Transformed Hosts, Development of Pharmaceuticals and Research Tools

Cells and animals that carry the HBM gene can be used as model systems to study and test for substances that have potential as therapeutic agents (Onyia et al, *J. Bone Miner. Res.*, 13:20-30 (1998); Broder et al, *Bone*, 21:225-235 (1997)). The cells are typically cultured mesenchymal stem cells. These may be isolated from individuals with somatic or germline HBM genes. Alternatively, the cell line can be engineered to carry the HBM gene, as described above. After a test substance is applied to the cells, the transformed phenotype of the cell is determined. Any trait of transformed cells can be assessed, including formation of bone matrix in culture (Broder et al, *Bone*, 21:225-235 (1997)), mechanical properties (Kizer et al, *Proc. Natl. Acad. Sci. USA*, 94:1013-1018 (1997)), and response to application of putative therapeutic agents.

Animals for testing therapeutic agents can be selected after treatment of germline cells or zygotes. Such treatments include insertion of the Zmax1 gene, as well as insertion of the HBM gene and disrupted homologous genes. Alternatively, the inserted Zmax1 gene(s) and/or HBM gene(s) of the animals may be disrupted by insertion or deletion mutation of other genetic alterations using conventional techniques, such as those described by, for example, Capechi, *Science*, 244:1288 (1989); Valancuis et al, *Mol. Cell Biol.*, 11:1402 (1991); Hasty et al, *Nature*, 350:243 (1991); Shinkai et al, *Cell*, 68:855 (1992); Mombaerts et al, *Cell*, 68:869 (1992); Philpott et al, *Science*, 256:1448 (1992); Snouwaert et al, *Science*, 257:1083 (1992); Donehower et al, *Nature*, 356:215 (1992). After test substances have been administered to the animals, the growth of bone must be assessed. If the test substance enhances the growth of bone, then the test substance is a candidate therapeutic agent. These animal models provide an extremely important vehicle for potential therapeutic products.

Individuals carrying the HBM gene have elevated bone mass. The HBM gene causes this phenotype by altering the activities, levels, expression patterns, and modification states of other molecules involved in bone development. Using a variety of established techniques, it is possible to identify molecules, preferably proteins or mRNAs, whose activities, levels, expression patterns, and modification states are different between systems containing the Zmax 1 gene and systems containing the HBM gene. Such systems can be, for example, cell-free extracts, cells, tissues or living organisms, such as mice or humans. For a mutant form of Zmax1, a complete deletion of Zmax1, mutations lacking the extracellular or intracellular portion of the protein, or any other mutation in the Zmax1 gene may be used. It is also possible to use expression of antisense Zmax1 RNA or oligonucleotides to inhibit production of the Zmax1 protein. For a mutant form of HBM, a complete deletion of HBM, mutations lacking the extracellular or intracellular portion of the HBM protein, or any other mutation in the HBM gene may be used. It is also possible to use expression of antisense HBM RNA or oligonucleotides to inhibit production of the HBM protein.

Molecules identified by comparison of Zmax1 systems and HBM systems can be used as surrogate markers in pharmaceutical development or in diagnosis of human or animal bone disease. Alternatively, such molecules may be used in treatment of bone disease. *See*, Schena et al, *Science*, 270:467-470 (1995).

For example, a transgenic mouse carrying the HBM gene in the mouse homologue is constructed. A mouse of the genotype HBM/+ is viable, healthy and has elevated bone mass. To identify surrogate markers for elevated bone mass, HBM/+ (i.e., heterozygous) and isogenic +/+ (i.e., wild-type) mice are sacrificed. Bone tissue mRNA is extracted from each animal, and a "gene chip" corresponding to mRNAs expressed in the +/+ individual is constructed. mRNA from different tissues is isolated from animals of each genotype, reverse-transcribed, fluorescently labeled, and then hybridized to gene fragments affixed to a solid support. The ratio of fluorescent intensity between the two populations is indicative of the relative abundance of the specific mRNAs in the +/+ and HBM/+ animals. Genes encoding

mRNAs over- and under-expressed relative to the wild-type control are candidates for genes coordinately regulated by the HBM gene.

One standard procedure for identification of new proteins that are part of the same signaling cascade as an already-discovered protein is as follows. Cells are treated with radioactive phosphorous, and the already-discovered protein is manipulated to be more ore less active. The phosphorylation state of other proteins in the cell is then monitored by polyacrylamide gel electrophoresis and autoradiography, or similar techniques. Levels of activity of the known protein may be manipulated by many methods, including, for example, comparing wild-type mutant proteins using specific inhibitors such as drugs or antibodies, simply adding or not adding a known extracellular protein, or using antisense inhibition of the expression of the known protein (Tamura et al, *Science*, 280(5369):1614-7 (1998); Meng, *EMBO J.*, 17(15):4391-403 (1998); Cooper et al, *Cell*, 1:263-73 (1982)).

In another example, proteins with different levels of phosphorylation are identified in TE85 osteosarcoma cells expressing either a sense or antisense cDNA for Zmax1. TE85 cells normally express high levels of Zmax1 (Dong et al, *Biochem. & Biophys. Res. Comm.*, 251:784-790 (1998)). Cells containing the sense construct express even higher levels of Zmax1, while cells expressing the antisense construct express lower levels. Cells are grown in the presence of ^{32}P, harvested, lysed, and the lysates run on SDS polyacrylamide gels to separate proteins, and the gels subjected to autoradiography (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1997)). Bands that differ in intensity between the sense and antisense cell lines represent phosphoproteins whose phosphorylation state or absolute level varies in response to levels of Zmax1. As an alternative to the ^{32}P-labeling, unlabeled proteins may be separated by SDS-PAGE and subjected to immunoblotting, using the commercially available anti-phosphotyrosine antibody as a probe (Thomas et al, *Nature*, 376(6537):267-71 (1995)). As an alternative to the expression of antisense RNA, transfection with chemically modified antisense oligonucleotides can be used (Woolf et al, *Nucleic Acids Res.*, 18(7):1763-9 (1990)).

Many bone disorders, such as osteoporosis, have a slow onset and a slow response to treatment. It is therefore useful to develop surrogate markers for bone

development and mineralization. Such markers can be useful in developing treatments for bone disorders, and for diagnosing patients who may be at risk for later development of bone disorders. Examples of preferred markers are N- and C-terminal telopeptide markers described, for example, in U.S. Patent Nos. 5,455,179, 5,641,837 and 5,652,112, the disclosures of which are incorporated by reference herein in their entirety. In the area of HIV disease, CD4 counts and viral load are useful surrogate markers for disease progression (Vlahov et al, *JAMA*, 279(1):35-40 (1998)). There is a need for analogous surrogate markers in the area of bone disease.

A surrogate marker can be any characteristic that is easily tested and relatively insensitive to non-specific influences. For example, a surrogate marker can be a molecule such as a protein or mRNA in a tissue or in blood serum. Alternatively, a surrogate marker may be a diagnostic sign such as sensitivity to pain, a reflex response or the like.

In yet another example, surrogate markers for elevated bone mass are identified using a pedigree of humans carrying the HBM gene. Blood samples are withdrawn from three individuals that carry the HBM gene, and from three closely related individuals that do not. Proteins in the serum from these individuals are electrophoresed on a two dimensional gel system, in which one dimension separates proteins by size, and another dimension separates proteins by isoelectric point (Epstein et al, *Electrophoresis*, 17(11):1655-70 (1996)). Spots corresponding to proteins are identified. A few spots are expected to be present in different amounts or in slightly different positions for the HBM individuals compared to their normal relatives. These spots correspond to proteins that are candidate surrogate markers. The identities of the proteins are determined by microsequencing, and antibodies to the proteins can be produced by standard methods for use in diagnostic testing procedures. Diagnostic assays for HBM proteins or other candidate surrogate markers include using antibodies described in this invention and a reporter molecule to detect HBM in human body fluids, membranes, bones, cells, tissues or extracts thereof. The antibodies can be labeled by joining them covalently or noncovalently with a substance that provides a detectable signal. In many scientific and patent literature, a variety of reporter molecules or labels are described including

radionuclides, enzymes, fluorescent, chemi-luminescent or chromogenic agents (U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241).

Using these antibodies, the levels of candidate surrogate markers are measured in normal individuals and in patients suffering from a bone disorder, such as osteoporosis, osteoporosis pseudoglioma, Engelmann's disease, Ribbing's disease, hyperphosphatasemia, Van Buchem's disease, melorheostosis, osteopetrosis, pychodysostosis, sclerosteosis, osteopoikilosis, acromegaly, Paget's disease, fibrous dysplasia, tubular stenosis, osteogenesis imperfecta, hypoparathyroidism, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, primary and secondary hyperparathyroidism and associated syndromes, hypercalciuria, medullary carcinoma of the thyroid gland, osteomalacia and other diseases. Techniques for measuring levels of protein in serum in a clinical setting using antibodies are well established. A protein that is consistently present in higher or lower levels in individuals carrying a particular disease or type of disease is a useful surrogate marker.

A surrogate marker can be used in diagnosis of a bone disorder. For example, consider a child that present to a physician with a high frequency of bone fracture. The underlying cause may be child abuse, inappropriate behavior by the child, or a bone disorder. To rapidly test for a bone disorder, the levels of the surrogate marker protein are measured using the antibody described above.

Levels of modification states of surrogate markers can be measured as indicators of the likely effectiveness of a drug that is being developed. It is especially convenient to use surrogate markers in creating treatments for bone disorders, because alterations in bone development or mineralization may require a long time to be observed. For example, a set of bone mRNAs, termed the "HBM-inducible mRNA set" is found to be overexpressed in HBM/+ mice as compared to +/+ mice, as described above. Expression of this set can be used as a surrogate marker. Specifically, if treatment of +/+ mice with a compound results in overexpression of the HBM-inducible mRNA set, then that compound is considered a promising candidate for further development.

This invention is particularly useful for screening compounds by using the Zmax1 or HBM protein or binding fragment thereof in any of a variety of drug screening techniques.

The Zmax1 or HBM protein or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the protein or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, for the formation of complexes between a Zmax1 or HBM protein or fragment and the agent being tested, or examine the degree to which the formation of a complex between a Zmax1 or HBM protein or fragment and a known ligand is interfered with by the agent being tested.

Thus, the present invention provides methods of screening for drugs comprising contacting such an agent with a Zmax1 or HBM protein or fragment thereof and assaying (i) for the presence of a complex between the agent and the Zmax1 or HBM protein or fragment, or (ii) for the presence of a complex between the Zmax1 or HBM protein or fragment and a ligand, by methods well known in the art. In such competitive binding assays the Zmax1 or HBM protein or fragment is typically labeled. Free Zmax1 or HBM protein or fragment is separated from that present in a protein:protein complex, and the amount of free (i.e., uncomplexed) label is a measure of the binding of the agent being tested to Zmax1 or HBM or its interference with Zmax1 or HBM: ligand binding, respectively.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the Zmax1 or HBM proteins and is described in detail in WO 84/03564. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with Zmax1 or HBM proteins and washed. Bound Zmax1 or HBM protein is then detected by methods well known in the art. Purified Zmax1 or HBM can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing

antibodies to the protein can be used to capture antibodies to immobilize the Zmax1 or HBM protein on the solid phase.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of specifically binding the Zmax1 or HBM protein compete with a test compound for binding to the Zmax1 or HBM protein or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants of the Zmax1 or HBM protein.

A further technique for drug screening involves the use of host eukaryotic cell lines or cells (such as described above) that have a nonfunctional Zmax1 or HBM gene. These host cell lines or cells are defective at the Zmax1 or HBM protein level. The host cell lines or cells are grown in the presence of drug compound. The rate of growth of the host cells is measured to determine if the compound is capable of regulating the growth of Zmax1 or HBM defective cells.

The goal of rational drug design is to produce structural analogs of biologically active proteins of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the protein, or which, e.g., enhance or interfere with the function of a protein *in vivo*. See, e.g., Hodgson, *Bio/Technology*, 9:19-21 (1991). In one approach, one first determines the three-dimensional structure of a protein of interest (e.g., Zmax1 or HBM protein) or, for example, of the Zmax1- or HBM-receptor or ligand complex, by x-ray crystallography, by computer modeling or most typically, by a combination of approaches. Less often, useful information regarding the structure of a protein may be gained by modeling based on the structure of homologous proteins. An example of rational drug design is the development of HIV protease inhibitors (Erickson et al, *Science,* 249:527-533 (1990)). In addition, peptides (e.g., Zmax1 or HBM protein) are analyzed by an alanine scan (Wells, *Methods in Enzymol.*, 202: 390-411 (1991)). In this technique, an amino acid residue is replaced by Ala, and its effect on the peptide's activity is determined. Each of the amino acid residues of the peptide is analyzed in this manner to determine the important regions of the peptide.

It is also possible to isolate a target-specific antibody, selected by a functional assay, and then to solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced banks of peptides. Selected peptides would then act as the pharmacore.

Thus, one may design drugs which have, e.g., improved Zmax1 or HBM protein activity or stability or which act as inhibitors, agonists, antagonists, etc. of Zmax1 or HBM protein activity. By virtue of the availability of cloned Zmax1 or HBM sequences, sufficient amounts of the Zmax1 or HBM protein may be made available to perform such analytical studies as x-ray crystallography. In addition, the knowledge of the Zmax1 or HBM protein sequence provided herein will guide those employing computer modeling techniques in place of, or in addition to x-ray crystallography.

XXI. Methods of Use: Avian and Mammalian Animal Husbandry

The Zmax1 DNA and Zmax1 protein and/or the HBM DNA and HBM protein can be used for vertebrate and preferably human therapeutic agents and for avian and mammalian veterinary agents, including for livestock breeding. Birds, including, for example, chickens, roosters, hens, turkeys, ostriches, ducks, pheasants and quails, can benefit from the identification of the gene and pathway for high bone mass. In many examples cited in literature (for example, McCoy et al, *Res. Vet. Sci.*, 60(2): 185-186 (1996)), weakened bones due to husbandry conditions cause cage layer fatigue, osteoporosis and high mortality rates. Additional therapeutic agents to treat osteoporosis or other bone disorders in birds can have considerable beneficial effects on avian welfare and the economic conditions of the livestock industry, including, for example, meat and egg production.

XXII. Methods of use: Diagnostic assays using Zmax1-specific oligonucleotides for detection of genetic alterations affecting bone development.

In cases where an alteration or disease of bone development is suspected to involve an alteration of the Zmax1 gene or the HBM gene, specific oligonucleotides may be constructed and used to assess the level of Zmax1 mRNA or HBM mRNA, respectively, in bone tissue or in another tissue that affects bone development.

For example, to test whether a person has the HBM gene, which affects bone density, polymerase chain reaction can be used. Two oligonucleotides are synthesized by standard methods or are obtained from a commercial supplier of custom-made oligonucleotides. The length and base composition are determined by standard criteria using the Oligo 4.0 primer Picking program (Wojchich Rychlik, 1992). One of the oligonucleotides is designed so that it will hybridize only to HBM DNA under the PCR conditions used. The other oligonucleotide is designed to hybridize a segment of Zmax1 genomic DNA such that amplification of DNA using these oligonucleotide primers produces a conveniently identified DNA fragment. For example, the pair of primers CCAAGTTCTGAGAAGTCC (SEQ ID NO:32) and AATACCTGAAACCATACCTG (SEQ ID NO:33) will amplify a 530 base pair DNA fragment from a DNA sample when the following conditions are used: step 1 at 95°C for 120 seconds; step 2 at 95°C for 30 seconds; step 3 at 58°C for 30 seconds; step 4 at 72°C for 120 seconds; where steps 2-4 are repeated 35 times. Tissue samples may be obtained from hair follicles, whole blood, or the buccal cavity.

The fragment generated by the above procedure is sequenced by standard techniques. Individuals heterozygous for the HBM gene will show an equal amount of G and T at the second position in the codon for glycine 171. Normal or homozygous wild-type individuals will show only G at this position.
Other amplification techniques besides PCR may be used as alternatives, such as ligation-mediated PCR or techniques involving Q-beta replicase (Cahill et al, *Clin. Chem.*, 37(9):1482-5 (1991)). For example, the oligonucleotides AGCTGCTCGT AGCTG TCTCTCCCTGGATCACGGGTACATGTACTGGACAGACTGGGT (SEQ ID NO:34) and TGAGACGCCCCGGATTGAGCGGGCAGGGATAGCTTA

TTCCCTGTGCCGCATTACGGC (SEQ ID NO:35) can be hybridized to a denatured human DNA sample, treated with a DNA ligase, and then subjected to PCR amplification using the primer oligonucleotides AGCTGCTCGTAGCTGTCT CTCCCTGGA (SEQ ID NO:36) and GCCGTAATGCGGCACAGGGAATAAGCT (SEQ ID NO:37). In the first two oligonucleotides, the outer 27 bases are random sequence corresponding to primer binding sites, and the inner 30 bases correspond to sequences in the Zmax1 gene. The T at the end of the first oligonucleotide corresponds to the HBM gene. The first two oligonucleotides are ligated only when hybridized to human DNA carrying the HBM gene, which results in the formation of an amplifiable 114 bp DNA fragment.

Products of amplification can be detected by agarose gel electrophoresis, quantitative hybridization, or equivalent techniques for nucleic acid detection known to one skilled in the art of molecular biology (Sambrook et al, *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratory, Cold Spring, NY (1989)).

Other alterations in the Zmax1 gene or the HBM gene may be diagnosed by the same type of amplification-detection procedures, by using oligonucleotides designed to identify those alterations. These procedures can be used in animals as well as humans to identify alterations in Zmax1 or HBM that affect bone development.

Expression of Zmax1 or HBM in bone tissue may be accomplished by fusing the cDNA of Zmax1or HBM, respectively, to a bone-specific promoter in the context of a vector for genetically engineering vertebrate cells. DNA constructs are introduced into cells by packaging the DNA into virus capsids, by the use of cationic liposomes, electroporation, or by calcium phosphate transfection. Transfected cells, preferably osteoblasts, may be studied in culture or may be introduced into bone tissue in animals by direct injection into bone or by intravenous injection of osteoblasts, followed by incorporation into bone tissue (Ko et al, *Cancer Research,* 56(20):4614-9 (1996)). For example, the osteocalcin promoter, which is specifically active in osteoblasts, may be used to direct transcription of the Zmax1 gene or the HBM gene. Any of several vectors and transfection methods may be used, such as retroviral vectors, adenovirus vectors, or vectors that are maintained after

transfection using cationic liposomes, or other methods and vectors described herein.

Alteration of the level of functional Zmax1 protein or HBM protein affects the level of bone mineralization. By manipulating levels of functional Zmax1 protein or HBM protein, it is possible to affect bone development and to increase or decrease levels of bone mineralization. For example, it may be useful to increase bone mineralization in patients with osteoporosis. Alternatively, it may be useful to decrease bone mineralization in patients with osteopetrosis or Paget's disease. Alteration of Zmax1 levels or HBM levels can also be used as a research tool. Specifically, it is possible to identify proteins, mRNA and other molecules whose level or modification status is altered in response to changes in functional levels of Zmax1 or HBM. The pathology and pathogenesis of bone disorders is known and described, for example, in Rubin and Farber (Eds.), *Pathology*, 2nd Ed., S.B. Lippincott Co., Philadelphia, PA (1994).

A variety of techniques can be used to alter the levels of functional Zmax1 or HBM. For example, intravenous or intraosseous injection of the extracellular portion of Zmax1 or mutations thereof, or HBM or mutations thereof, will alter the level of Zmax1 activity or HBM activity, respectively, in the body of the treated human, animal or bird. Truncated versions of the Zmax1 protein or HBM protein can also be injected to alter the levels of functional Zmax1 protein or HBM protein, respectively. Certain forms of Zmax1 or HBM enhance the activity of endogenous protein, while other forms are inhibitory.

In a preferred embodiment, the HBM protein is used to treat osteoporosis. In a further preferred embodiment, the extracellular portion of the HBM protein is used. This HBM protein may be optionally modified by the addition of a moiety that causes the protein to adhere to the surface of cells. The protein is prepared in a pharmaceutically acceptable solution and is administered by injection or another method that achieves acceptable pharmacokinetics and distribution.

In a second embodiment of this method, Zmax1 or HBM levels are increased or decreased by gene therapy techniques. To increase Zmax1 or HBM levels, osteoblasts or another useful cell type are genetically engineered to express high

levels of Zmax1 or HBM as described above. Alternatively, to decrease Zmax1 or HBM levels, antisense constructs that specifically reduce the level of translatable Zmax1 or HBM mRNA can be used. In general, a tissue-nonspecific promoter may be used, such as the CMV promoter or another commercially available promoter found in expression vectors (Wu et al, *Toxicol. Appl. Pharmacol.*, 141(1):330-9 (1996)). In a preferred embodiment, a Zmax1 cDNA or its antisense is transcribed by a bone-specific promoter, such as the osteocalcin or another promoter, to achieve specific expression in bone tissue. In this way, if a Zmax1-expressing DNA construct or HBM-expressing construct is introduced into non-bone tissue, it will not be expressed.

In a third embodiment of this method, antibodies against Zmax1 or HBM are used to inhibit its function. Such antibodies are identified herein.

In a fourth embodiment of this method, drugs that inhibit Zmax1 function or HBM function are used. Such drugs are described herein and optimized according to techniques of medicinal chemistry well known to one skilled in the art of pharmaceutical development.

Zmax1 and HBM interact with several proteins, such as ApoE. Molecules that inhibit the interaction between Zmax1 or HBM and ApoE or another binding partner are expected to alter bone development and mineralization. Such inhibitors may be useful as drugs in the treatment of osteoporosis, osteopetrosis, or other diseases of bone mineralization. Such inhibitors may be low molecular weight compounds, proteins or other types of molecules. *See*, Kim et al, *J. Biochem.* (Tokyo), 124(6):1072-1076 (1998).

Inhibitors of the interaction between Zmax1 or HBM and interacting proteins may be isolated by standard drug-screening techniques. For example, Zmax1 protein, (or a fragment thereof) or HBM protein (or a fragment thereof) can be immobilized on a solid support such as the base of microtiter well. A second protein or protein fragment, such as ApoE is derivatized to aid in detection, for example with fluorescein. Iodine, or biotin, then added to the Zmax1 or HBM in the presence of candidate compounds that may specifically inhibit this protein-protein domain of Zmax1 or HBM, respectively, and thus avoid problems associated with its

transmembrane segment. Drug screens of this type are well known to one skilled in the art of pharmaceutical development.

Because Zmax1 and HBM are involved in bone development, proteins that bind to Zmax1 and HBM are also expected to be involved in bone development. Such binding proteins can be identified by standard methods, such as co-immunoprecipitation, co-fractionation, or the two-hybrid screen (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1997)). For example, to identify Zmax1-interacting proteins or HBM-interacting proteins using the two-hybrid system, the extracellular domain of Zmax1 or HBM is fused to LexA and expressed for the yeast vector pEG202 (the "bait") and expressed in the yeast strain EGY48. The yeast strain is transformed with a "prey" library in the appropriate vector, which encodes a galactose-inducible transcription-activation sequence fused to candidate interacting proteins. The techniques for initially selecting and subsequently verifying interacting proteins by this method are well known to one skilled in the art of molecular biology (Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons (1997)).

In a preferred embodiment, proteins that interact with HBM, but not Zmax1, are identified using a variation of the above procedure (Xu et al, *Proc. Natl. Acad. Sci. USA,* 94(23):12473-8 (Nov. 1997)). This variation of the two-hybrid system uses two baits, and Zmax1 and HBM are each fused to LexA and TetR, respectively. Alternatively, proteins that interact with the HBM but not Zmax1 are also isolated. These procedures are well known to one skilled in the art of molecular biology, and are a simple variation of standard two-hybrid procedures.

As an alternative method of isolating Zmax1 or HBM interacting proteins, a biochemical approach is used. The Zmax1 protein or a fragment thereof, such as the extracellular domain, or the HBM protein or a fragment thereof, such as the extracellular domain, is chemically coupled to Sepharose beads. The Zmax1- or HBM-coupled beads are poured into a column. An extract of proteins, such as serum proteins, proteins in the supernatant of a bone biopsy, or intracellular proteins from gently lysed TE85 osteoblastic cells, is added to the column. Non-specifically bound proteins are eluted, the column is washed several times with a low-salt buffer,

and then tightly binding proteins are eluted with a high-salt buffer. These are candidate proteins that bind to Zmax1 or HBM, and can be tested for specific binding by standard tests and control experiments. Sepharose beads used for coupling proteins and the methods for performing the coupling are commercially available (Sigma), and the procedures described here are well known to one skilled in the art of protein biochemistry.

As a variation of the above procedure, proteins that are eluted by high salt from the Zmax1- or HBM-Sepharose column are then added to an HBM-Zmax1-sepharose column. Proteins that flow through without sticking are proteins that bind to Zmax1 but not to HBM. Alternatively, proteins that bind to the HBM protein and not to the Zmax1 protein can be isolated by reversing the order in which the columns are used.

XXIII. Method of Use: Transformation-Associated Recombination (TAR) Cloning

Essential for the identification of novel allelic variants of Zmax1 is the ability to examine the sequence of both copies of the gene in an individual. To accomplish this, two "hooks," or regions of significant similarity, are identified within the genomic sequence such that they flank the portion of DNA that is to be cloned. Most preferably, the first of these hooks is derived from sequences 5' to the first exon of interest and the second is derived from sequences 3' to the last exon of interest. These two "hooks" are cloned into a bacterial/yeast shuttle vector such as that described by Larionov et al, *Proc. Natl. Acad. Sci. USA*, 94:7384-7387 (1997). Other similar vector systems may also be used. To recover the entire genomic copy of the Zmax1 gene, the plasmid containing the two "hooks" is linearized with a restriction endonuclease or is produced by another method such as PCR. This linear DNA fragment is introduced into yeast cells along with human genomic DNA. Typically, the yeast *Saccharomyces cerevisiae* is used as a host cell, although Larionov et al (in press) have reported using chicken host cells as well. During and after the process of transformation, the endogenous host cell converts the linear plasmid to a circle by a recombination event whereby the region of the human genomic DNA homologous to the "hooks" is inserted into the plasmid. This

plasmid can be recovered and analyzed by methods well known to one skilled in the art. Obviously, the specificity for this reaction requires the host cell machinery to recognize sequences similar to the "hooks" present in the linear fragment. However, 100% sequence identity is not required, as shown by Kouprina et al, *Genomics*, 53(1):21-28 (October 1998), where the author describes using degenerate repeated sequences common in the human genome to recover fragments of human DNA from a rodent/human hybrid cell line.

In another example, only one "hook" is required, as described by Larionov et al, *Proc. Natl. Acad. Sci. USA*, 95(8):4469-74 (April 1998). For this type of experiment, termed "radial TAR cloning," the other region of sequence similarity to drive the recombination is derived from a repeated sequence from the genome. In this way, regions of DNA adjacent to the Zmax1 gene coding region can be recovered and examined for alterations that may affect function.

XXIV. Methods of Use: Genomic Screening

The use of polymorphic genetic markers linked to the HBM gene or to Zmax1 is very useful in predicting susceptibility to osteoporosis or other bone diseases. Koller et al, *Amer. J. Bone Min. Res.*, 13:1903-1908 (1998) have demonstrated that the use of polymorphic genetic markers is useful for linkage analysis. Similarly, the identification of polymorphic genetic markers within the high bone mass gene will allow the identification of specific allelic variants that are in linkage disequilibrium with other genetic lesions that affect bone development. Using the DNA sequence from the BACs, a dinucleotide CAn repeat was identified and two unique PCR primers that will amplify the genomic DNA containing this repeat were designed, as shown below:

B200E21C16_L: GAGAGGCTATATCCCTGGGC (SEQ ID NO:38)
B200E21C16_R: ACAGCACGTGTTTAAAGGGG (SEQ ID NO:39)

and used in the genetic mapping study.

This method has been used successfully by others skilled in the art (e.g., Sheffield et al, *Genet.*, 4:1837-1844 (1995); LeBlanc-Straceski et al, *Genomics*, 19:341-9 (1994); Chen et al, *Genomics*, 25:1-8 (1995)). Use of these reagents with populations or individuals will predict their risk for osteoporosis. Similarly, single

nucleotide polymorphisms (SNPs), such as those shown in Table 4 above, can be used as well to predict risk for developing bone diseases or resistance to osteoporosis in the case of the HBM gene.

XXV. Methods of Use: Modulators of Tissue Calcification

The calcification of tissues in the human body is well documented. Towler et al, *J. Biol. Chem.*, 273:30427-34 (1998) demonstrated that several proteins known to regulate calcification of the developing skull in a model system are expressed in calcified aorta. The expression of Msx2, a gene transcribed in osteoprogenitor cells, in calcified vascular tissue indicates that genes which are important in bone development are involved in calcification of other tissues. Treatment with HBM protein, agonists or antagonists is likely to ameliorate calcification (such as the vasculature, dentin and bone of the skull visera) due to its demonstrated effect on bone mineral density. In experimental systems where tissue calcification is demonstrated, the over-expression or repression of Zmax1 activity permits the identification of molecules that are directly regulated by the Zmax1 gene. These genes are potential targets for therapeutics aimed at modulating tissue calcification. For example, an animal, such as the LDLR -/-, mouse is fed a high fat diet and is observed to demonstrate expression of markers of tissue calcification, including Zmax1. These animals are then treated with antibodies to Zmax1 or HBM protein, antisense oligonucleotides directed against Zmax1 or HBM cDNA, or with compounds known to bind the Zmax1 or HBM protein or its binding partner or ligand. RNA or proteins are extracted from the vascular tissue and the relative expression levels of the genes expressed in the tissue are determined by methods well known in the art. Genes that are regulated in the tissue are potential therapeutic targets for pharmaceutical development as modulators of tissue calcification.

The nucleic acids, proteins, peptides, amino acids, small molecules or other pharmaceutically useful compounds of the present invention that are to be given to an individual may be administered in the form of a composition with a pharmaceutically acceptable carrier, excipient or diluent, which are well known in the art. The individual may be a mammal or a bird, preferably a human, a rat, a mouse or bird. Such compositions may be administered to an individual in a

pharmaceutically effective amount. The amount administered will vary depending on the condition being treated and the patient being treated. The compositions may be administered alone or in combination with other treatments.

EXAMPLES

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

Example 1

The propositus was referred by her physicians to the Creighton Osteoporosis Center for evaluation of what appeared to be unusually dense bones. She was 18 years old and came to medical attention two years previous because of back pain, which was precipitated by an auto accident in which the car in which she was riding as a passenger was struck from behind. Her only injury was soft tissue injury to her lower back that was manifested by pain and muscle tenderness. There was no evidence of fracture or subluxation on radiographs. The pain lasted for two years, although she was able to attend school full time. By the time she was seen in the Center, the pain was nearly resolved and she was back to her usual activities as a high school student. Physical exam revealed a normal healthy young woman standing 66 inches and weighing 128 pounds. Radiographs of the entire skeleton revealed dense looking bones with thick cortices. All bones of the skeleton were involved. Most importantly, the shapes of all the bones were entirely normal. The spinal BMC was 94.48 grams in L1-4, and the spinal BMD was 1.667 gm/cm^2 in L1-4. BMD was 5.62 standard deviations (SD) above peak skeletal mass for women. These were measured by DXA using a Hologic 2000~. Her mother was then scanned and a lumbar spinal BMC of 58.05 grams and BMD of 1.500 gm/cm^2 were found. Her mother's values place her 4.12 SD above peak mass and 4.98 SD above her peers. Her mother was 51 years old, stood 65 inches and weighed 140 pounds. Her mother was in excellent health with no history of musculoskeletal or other symptoms. Her father's lumbar BMC was 75.33 grams and his BMD was

1.118 gm/cm^2. These values place him 0.25 SD above peak bone mass for males. He was in good health, stood 72 inches tall, and weighed 187 pounds.

These clinical data suggested that the propositus inherited a trait from her mother, which resulted in very high bone mass, but an otherwise normal skeleton, and attention was focused on the maternal kindred. In U.S. Patent No. 5,691,153, twenty- two of these members had measurement of bone mass by DXA. In one case, the maternal grandfather of the propositus, was deceased, however, medical records, antemortem skeletal radiographs and a gall bladder specimen embedded in paraffin for DNA genotyping were obtained. His radiographs showed obvious extreme density of all of the bones available for examination including the femur and the spine, and he was included among the affected members. In this invention, the pedigree has been expanded to include 37 informative individuals. These additions are a significant improvement over the original kinship (Johnson et al, *Am. J. Hum. Genet.*, 60:1326-1332 (1997)) because, among the fourteen individuals added since the original study, two individuals harbor key crossovers. X-linkage is ruled out by the presence of male-to-male transmission from individual 12 to 14 and 15.

Example 2

The present invention describes DNA sequences derived from two BAC clones from the HBM gene region, as evident in Table 7 below, which is an assembly of these clones. Clone b200e21-h (ATCC No. 980812; SEQ ID NOS: 10-11) was deposited at the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 U.S.A., on December 30, 1997. Clone b527d12-h (ATCC No. 980720; SEQ ID NOS: 5-9) was deposited at the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 U.S.A., on October 2, 1998. These sequences are unique reagents that can be used by one skilled in the art to identify DNA probes for the Zmax1 gene, PCR primers to amplify the gene, nucleotide polymorphisms in the Zmax1 gene, or regulatory elements of the Zmax1 gene.

TABLE 7

Contig	ATCC No.	SEQ ID NO.	Length (base pairs)
b527d12-h_contig302G	980720	5	3096
b527d12-h_contig306G	980720	6	26928
b527d12-h_contig307G	980720	7	29430
b527d12-h_contig308G	980720	8	33769
b527d12-h_contig309G	980720	9	72049
b200e21-h_contig1	980812	10	8705
b200e21-h_contig4	980812	11	66933

The disclosure of each of the patents, patent applications and publications cited in the specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will recognize that numerous changes and modifications can be made, and that such changes and modifications may be made without departing from the spirit and scope of the invention.

This application claims priority to U.S. Application Nos. 09/543,771 and 09/544,398 filed on April 5, 2000, which are a continuation-in-part of Application No. 09/229,319, filed January 13, 1999, which claims benefit of U.S. Provisional Application No. 60/071,449, filed January 13, 1998, and U.S. Provisional Application No. 60/105,511, filed October 23, 1998, all of which are herein incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. An isolated nucleic acid sequence of SEQ ID NO: 2.

2. The isolated nucleic acid sequence of claim 1, wherein the nucleic acid sequence is DNA.

3. An isolated amino acid sequence of SEQ ID NO: 4.

4. A nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:4.

5. A replicative cloning vector comprising the nucleic acid sequence of claim 1 and a replicon operative in an isolated host cell.

6. An isolated host cell transformed with the replicative cloning vector of claim 5.

7. An expression vector comprising the nucleic acid sequence of claim 1 operably linked to a transcription regulatory region.

8. An isolated host cell transformed with the expression vector of claim 7.

9. A method for testing a substance as a therapeutic agent for bone modulation in a host comprising administering the nucleic acid of claim 1 to the host, and assessing whether bone modulation occurs.

10. The method of claim 9, wherein the host is a cell or an animal.

11. The method of claim 10, wherein the animal is a human, a rodent or a bird.

12. A method of identifying a molecule involved in bone modulation comprising identifying a molecule that binds to, or that inhibits binding of a molecule to, HBM.

13. The method of claim 12, wherein said molecule is a protein.

14. A method for identifying a protein involved in bone modulation comprising identifying a protein that has an expression level that is different in a first host comprising the Zmax1 gene when compared to a second host comprising the HBM gene.

15. The method of claim 14, wherein the host is a cell or an animal.

16. A method of identifying a candidate protein involved in bone modulation comprising

identifying a protein in a first individual having the high bone mass phenotype;

identifying a protein in a second individual not having the high bone mass phenotype;

comparing the protein of the first individual to the protein of the second individual, wherein (i) the protein that is present in the first individual but not the second individual is the candidate protein or (ii) the protein that is present in a higher amount in the first individual than in the second individual is the candidate protein or (iii) the protein that is present in a lower amount in the first individual than in the second individual is the candidate protein.

17. The method of claim 16, further comprising producing an antibody to the candidate protein.

18. A method of identifying a candidate protein involved in bone modulation comprising

identifying a protein in a first individual having the high bone mass phenotype;

identifying a protein in a second individual not having the high bone mass phenotype; and

comparing the protein of the first individual to the protein of the second individual, wherein (i) the protein that is present in the second individual but not the first individual is the candidate protein or (ii) the protein that is present in a higher amount in the second individual than in the first individual is the candidate protein or (iii) the protein that is present in a lower amount in the second individual than in the first individual is the candidate protein.

19. The method of claim 18, further comprising producing an antibody to the candidate protein.

20. A method of testing for HBM activity comprising immobilizing an HBM protein, binding a protein to the HBM protein, and measuring the extent of binding.

21. The method of claim 20, wherein the protein is ApoE.

22. A method for identification of a candidate molecule involved in bone modulation comprising

identifying a molecule that binds to, or that inhibits binding of a molecule to, the nucleic acid sequence of SEQ ID NO: 1;

identifying a molecule that binds to, or that inhibits binding of a molecule to, the nucleic acid sequence of SEQ ID NO: 2; and

comparing the extent of binding, or the extent of inhibition of binding, of the molecule to each nucleic acid sequence, wherein the molecule that binds, or inhibits

binding, more or less to the nucleic acid sequence of SEQ ID NO: 2 or the nucleic acid sequence of SEQ ID NO: 1 is the candidate molecule.

23. The method of claim 22, wherein the candidate molecule is a protein or an mRNA.

24. A method of pharmaceutical development for treatment of bone development disorders comprising identifying a molecule that binds to the amino acid sequence of SEQ ID NO: 4.

25. The method of claim 24, wherein the molecule inhibits or enhances the function of the amino acid.

26. A method of pharmaceutical development for treatment of bone development disorders comprising

constructing a first host that contains the Zmax1 gene or protein;

constructing a second host that contains the HBM gene or protein;

analyzing a difference between the first host and the second host;

identifying a molecule that, when added to the first host, causes the first host to exhibit a characteristic feature of the second host.

27. The method of claim 26, wherein the host is a cell-free extract, a cell or an animal.

28. The method of claim 26, wherein the difference is a surrogate marker.

29. A method for treating a bone development disorder in an animal comprising transferring the nucleic acid sequence of claim 1 into a somatic cell of an animal suffering from a bone development disorder.

30. The method of claim 29, wherein the animal is a human or a bird.

31. A method for treating a bone development disorder in an animal comprising transferring the nucleic acid sequence of claim 1 into a germ-line cell of an animal suffering from a bone development disorder.

32. The method of claim 31, wherein the animal is a human or a bird.

33. A method of altering bone development in a host comprising administering the amino acid sequence of claim 3 to a somatic cell of a host suffering from a bone development disorder.

34. The method of claim 33, wherein the host is a human or a bird.

35. A method of altering bone development in a host comprising administering the amino acid sequence of claim 3 to a germ-line cell in a host suffering from a bone development disorder.

36. The method of claim 35, wherein the animal is a human or a bird.

37. A method of treating osteoporosis comprising administering the amino acid sequence of claim 3 to a patient in need thereof.

38. The method of claim 37, wherein the patient is a human or a bird.

39. A method of treating osteoporosis comprising administering the extracellular domain of the amino acid sequence of claim 3 to a patient in need thereof.

40. The method of claim 39, wherein the patient is a human or a bird.

41. A method of treating osteoporosis comprising administering the intracellular domain of the amino acid sequence of claim 3 to a patient in need thereof.

42. The method of claim 41, wherein the patient is a human or a bird.

43. A method for treating bone development disorders comprising administering a molecule that binds to the nucleic acid sequence of claim 1 to a patient in need thereof.

44. The method of claim 43, wherein the patient is a human or a bird.

45. A method for treating bone development disorders comprising administering an antibody to a patient in need thereof, wherein the antibody is to the amino acid sequence of claim 3.

46. A method for diagnostic screening for a genetic predisposition to a bone development disorder comprising screening a sample from a patient with a nucleotide sequence derived from the genomic or cDNA nucleic acid sequence of HBM.

47. A diagnostic assay for bone development disorders comprising an antibody to the HBM protein.

48. A method for identifying a genetic predisposition to bone development disorders comprising performing a haplotype analysis using the nucleic acid sequence of claim 1.

49. A method of expressing the HBM protein in bone tissue comprising constructing an expression vector comprising a promoter that directs expression in bone tissue operably linked to the nucleic acid sequence of claim 1.

50. The method of claim 49, wherein the promoter that directs expression in bone is an osteocalcin promoter, a bone sialoprotein promoter or an AML-3 promoter.

51. A bacterial artificial chromosome having the nucleic acid sequence of SEQ ID NO: 5, 6, 7, 8, 9, 10 or 11.

52. A method for amplifying a nucleotide polymorphism in the Zmax1 gene comprising using the bacterial artificial chromosome of claim 51.

53. A method for amplifying a nucleotide polymorphism in the HBM gene comprising using the bacterial artificial chromosome of claim 51.

54. A method for identifying a regulatory element of a HBM gene comprising using the bacterial artificial chromosome of claim 1 or claim 51.

55. An isolated nucleic acid sequence comprising at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2, wherein one of the at least 15 contiguous nucleotides is thymine at position 582.

56. The isolated nucleic acid sequence of claim 55 that is DNA.

57. The isolated nucleic acid sequence of claim 55 that is RNA.

58. A replicative cloning vector comprising the nucleic acid sequence of claim 55 and a replicon operative in a host cell.

59. An isolated host cell transformed with the replicative cloning vector of claim 58.

60. An expression vector comprising the nucleic acid sequence of claim 55 operably linked to a transcription regulatory region.

61. An isolated host cell transformed with the expression vector of claim 60.

62. An isolated nucleic acid sequence comprising at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2, wherein one of the at least 15 contiguous nucleotides is thymine at position 582, and which encodes for an amino acid sequence including a valine corresponding to valine at position 171 of SEQ ID NO: 4.

63. The nucleic acid sequence of claim 62 which is DNA.

64. An isolated nucleic acid segment of at least 15 contiguous nucleotides including a polymorphic site from the nucleic acid sequence of SEQ ID NO: 2 in which G at position 582 is replaced by T, and sequences complementary thereto.

65. The isolated nucleic acid segment of claim 64, wherein said complementary sequence is the reverse complement.

66. The isolated nucleic acid segment of claim 65, wherein said reverse complementary sequence is mRNA.

67. The isolated nucleic acid segment of claim 64 that is DNA.

68. The isolated nucleic acid segment of claim 64 that is cDNA.

69. The isolated nucleic acid segment of claim 65 that is RNA.

70. An isolated nucleic acid segment of at least 15 contiguous nucleotides including a single nucleotide polymorphic site from an exon sequence selected from the group consisting of:

SEQ ID NO: 9 wherein nucleotide 69169 is replaced by A,

SEQ ID NO: 9 wherein nucleotide 27402 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 27841 is replaced by C,

SEQ ID NO: 9 wherein nucleotide 35600 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 45619 is replaced by A,

SEQ ID NO: 9 wherein nucleotide 46018 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 46093 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 46190 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 50993 is replaced by C,

SEQ ID NO: 9 wherein nucleotide 51124 is replaced by T,

SEQ ID NO: 9 wherein nucleotide 55461 is replaced by T,

SEQ ID NO: 9 wherein nucleotide 63645 is replaced by A,

SEQ ID NO: 9 wherein nucleotide 63646 is replaced by C,

SEQ ID NO: 9 wherein nucleotide 24809 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 27837 is replaced by C,

SEQ ID NO: 9 wherein nucleotide 31485 is replaced by T,

SEQ ID NO: 9 wherein nucleotide 31683 is replaced by G,

SEQ ID NO: 9 wherein nucleotide 24808 is replaced by G,

SEQ ID NO: 8 wherein nucleotide 31340 is replaced by C,

SEQ ID NO: 8 wherein nucleotide 32538 is replaced by G,

SEQ ID NO: 8 wherein nucleotide 13224 is replaced by G,

SEQ ID NO: 8 wherein nucleotide 21119 is replaced by A,

SEQ ID NO: 8 wherein nucleotide 30497 is replaced by A,

SEQ ID NO: 9 wherein nucleotide 24811 is replaced by C,

SEQ ID NO: 9 wherein nucleotide 68280 is replaced by A, and

sequences complementary thereto.

71. The isolated nucleic acid segment of claim 70, wherein nucleotide 21119 of said exon sequence of SEQ ID NO: 8 is replaced by A.

72. The isolated nucleic acid segment of claim 70 that is DNA.

73. The isolated nucleic acid segment of claim 70 that is RNA.

74. The isolated nucleic acid segment of claim 64 or claim 70 which is a probe or a primer.

75. A method of identifying a molecule involved in bone modulation comprising identifying a molecule that binds to or that inhibits binding of a molecule to a protein involved in focal adhesion signaling.

76. The method of claim 75, wherein the molecule involved in focal adhesion signaling binds to a protein selected from the group consisting of: SEQ ID NO: 87-109.

77. The method of claim 75, wherein the molecule involved in focal adhesion signaling binds to a protein selected from the group consisting of: SEQ ID NO:90, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:99 and SEQ ID NO:102.

78. A method of modulating bone density in a subject by administering an agent that regulates a nucleic acid or polypeptide encoded thereby involved in focal adhesion signaling.

79. The method of claim 78, wherein the nucleic acid comprises a nucleic acid selected from the group consisting of: SEQ ID NOS: 63-86.

80. The method of claim 78, wherein the nucleic acid comprises SEQ ID NO: 66, SEQ ID NO: 71, SEQ ID NO: 77 or SEQ ID NO: 79.

81. The method of claim 78, wherein the polypeptide is selected from the group consisting of: SEQ ID NOS: 87-109.

82. The method of claim 78, wherein the polypeptide is SEQ ID NO:90, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:99 or SEQ ID NO:102.

83. A nucleic acid comprising SEQ ID NO: 66, SEQ ID NO: 71, SEQ ID NO: 77 or SEQ ID NO: 79.

84. A nucleic acid of claim 83, wherein the nucleic acid is RNA or DNA.

85. A replicative cloning vector comprising a nucleic acid of claim 83 and a replicon operative in a host cell.

86. An isolated host cell transformed with the replicative cloning vector of claim 85.

87. An expression vector comprising the nucleic acid sequence of claim 83.

88. An isolated host cell transformed with the expression vector of claim 87.

89. A polypeptide comprising SEQ ID NO:90, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:99 or SEQ ID NO:102.

90. A nucleic acid encoding a polypeptide selected from the group consisting of SEQ ID NO:90, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:99 or SEQ ID NO:102.

91. A method of treating bone development disorders comprising the step of administering an agent which modulates a nucleic acid or a polypeptide involved in focal adhesion signaling.

92. The method of claim 91, wherein the nucleic acid modulated by the agent is selected from any one of SEQ ID NOS: 63-86.

93. The method of claim 91, wherein the polypeptide modulated by the agent is selected from any one of SEQ ID NOS: 87-109.

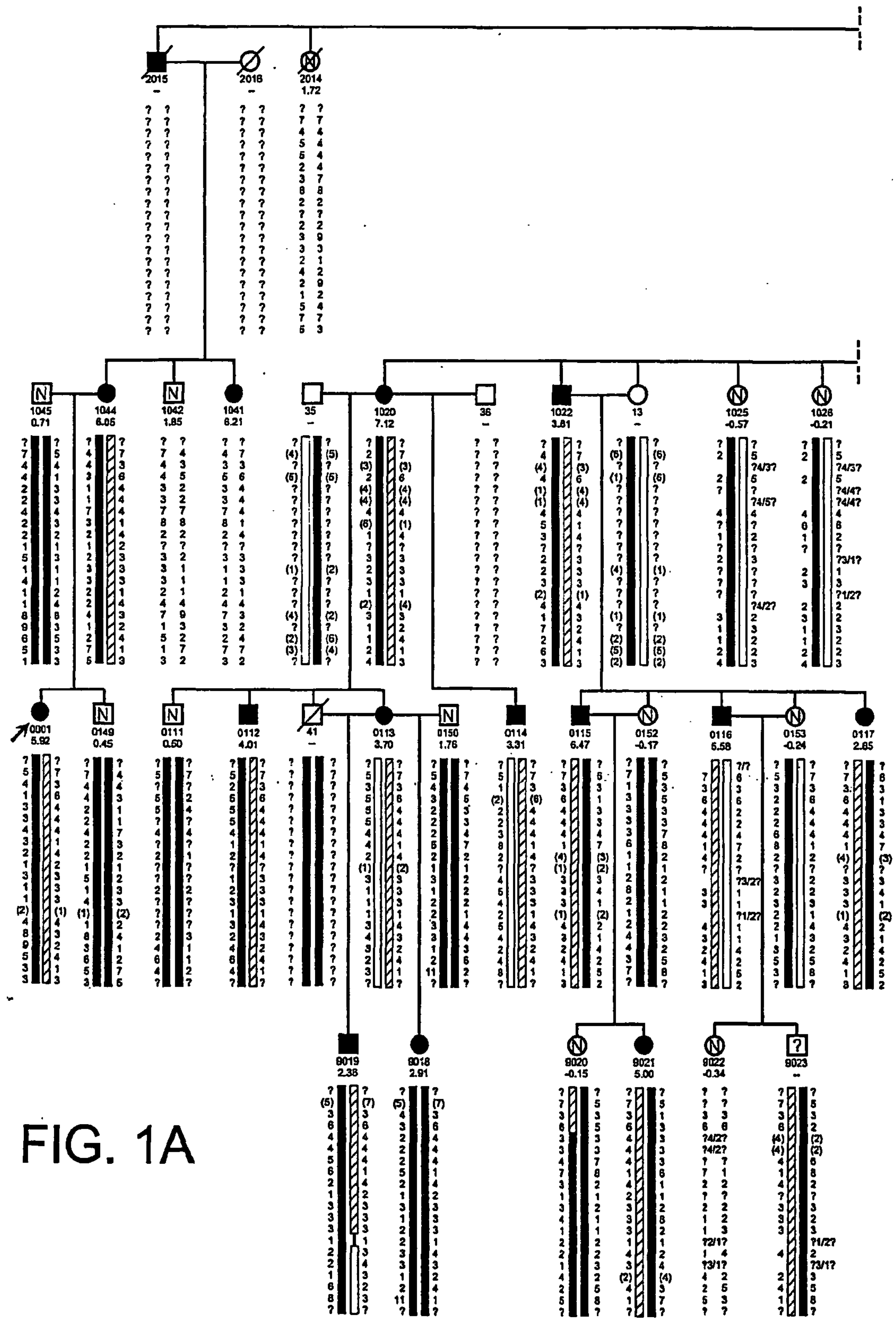


FIG. 1A

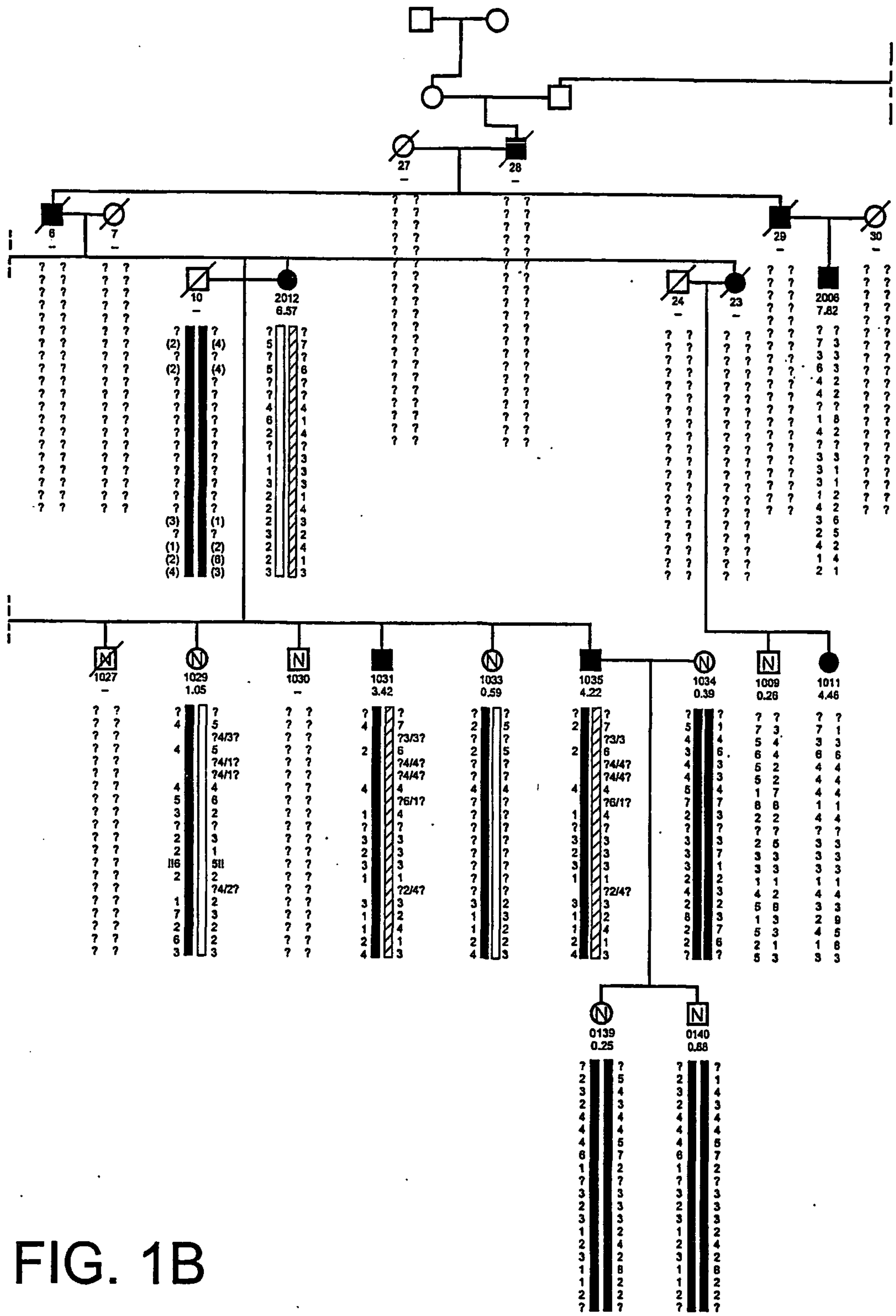


FIG. 1B

FIG. 2A

BAC/STS Map of the HBM Region

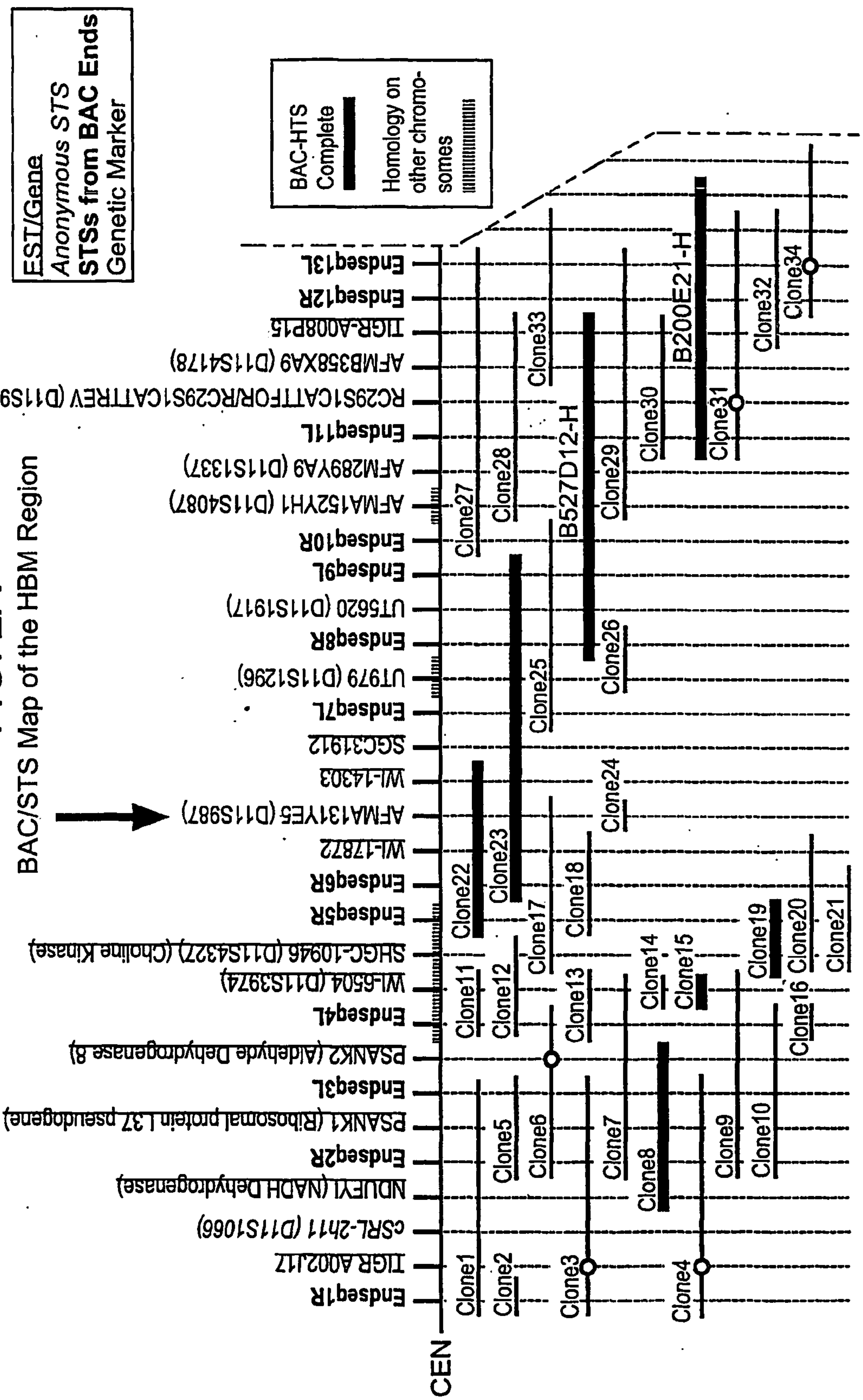
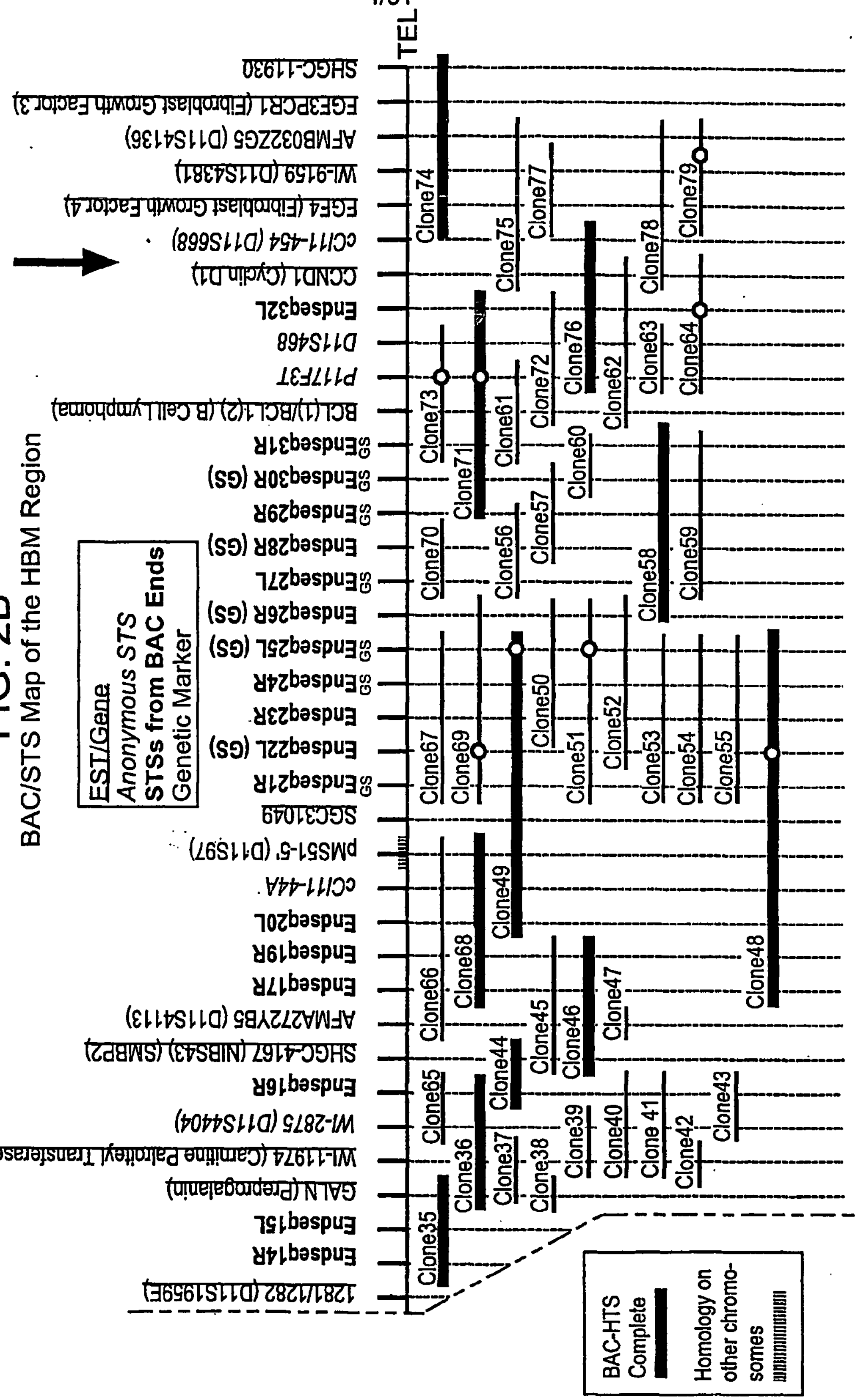


FIG. 2B
BAC/STS Map of the HBM Region



Exon 1
ACTAAAGCGCCGCCGCCGCGCCATGGAGCCCGAGTGAGCGCGGCGCGG
GCCCGTCCGGCCGCCGGACAACATGGAGGCAGCGCCGCCCGGGCCGCC
GTGGCCGCTGCTGCTGCTGCTGCTGCTGCTGCTGGCGCTGTGCGGCTGC
CCGGCCCCCGCCGCGGCC

Exon 2 Coordinates: 527d12_Contig308G 30944-30549
gccccacagCCTCGCCGCTCCTGCTATTTGCCAACCGCCGGGACGTACGGCT
GGTGGACGCCGGCGGAGTCAAGCTGGAGTCCACCATCGTGGTCAGCGG
CCTGGAGGATGCGGCCGCAGTGGACTTCCAGTTTTCCAAGGGAGCCGTG
TACTGGACAGACGTGAGCGAGGAGGCCATCAAGCAGACCTACCTGAACC
AGACGGGGGCCGCCGTGCAGAACGTGGTCATCTCCGGCCTGGTCTCTCC
CGACGGCCTCGCCTGCGACTGGGTGGGCAAGAAGCTGTACTGGACGGA
CTCAGAGACCAACCGCATCGAGGTGGCCAACCTCAATGGCACATCCCGG
AAGGTGCTCTTCTGGCAGGACCTTGACCAGCCGAGGGCCATCGCCTTGG
ACCCCGCTCACGGgtaaaccctgctg

... 9408 nt ...

Exon 3 Coordinates: 527d12_Contig308G 21141-20945
ccccgtcacagGTACATGTACTGGACAGACTGGGGTGAGACGCCCCGGATTGA
GCGGGCAGGGATGGATGGCAGCACCCGGAAGATCATTGTGGACTCGGA
CATTTACTGGCCCAATGGACTGACCATCGACCTGGAGGAGCAGAAGCTC
TACTGGGCTGACGCCAAGCTCAGCTTCATCCACCGTGCCAACCTGGACG
GCTCGTTCCGgtaggtacccac

... 6094 nt ...

Exon 4 Coordinates: 527d12_Contig308G 15047-14850
tccctgactgcagGCAGAAGGTGGTGGAGGGCAGCCTGACGCACCCCTTCGCCC
TGACGCTCTCCGGGGACACTCTGTACTGGACAGACTGGCAGACCCGCTC
CATCCATGCCTGCAACAAGCGCACTGGGGGGAAGAGGAAGGAGATCCTG
AGTGCCCTATACTCACCCATGGACATCCAGGTGCTGAGCCAGGAGCGGC
AGCCTTTCTgtgagtgccgg

... 1827 nt ...

Exon 5 Coordinates: 527d12_Contig308G 13220-13088
tttctcagTCCACACTCGCTGTGAGGAGGACAATGGCGGCTGCTCCCACCTGT
GCCTGCTGTCCCCAAGCGAGCCTTTCTACACATGCGCCTGCCCCACGGG
TGTGCAGCTGCAGGACAACGGCAGGACGTGTAAGGCAGgtgaggcggtgggacg

FIG. 3A

... 20923 nt ...

Exon 6 Coordinates: 527d12_Contig309G 7705-8100
ctccacagGAGCCGAGGAGGTGCTGCTGCTGGCCCGGCGGACGGACCTACG
GAGGATCTCGCTGGACACGCCGGACTTCACCGACATCGTGCTGCAGGTG
GACGACATCCGGCACGCCATTGCCATCGACTACGACCCGCTAGAGGGCT
ATGTCTACTGGACAGATGACGAGGTGCGGGCCATCCGCAGGGCGTACCT
GGACGGGTCTGGGGCGCAGACGCTGGTCAACACCGAGATCAACGACCC
CGATGGCATCGCGGTCGACTGGGTGGCCCGAAACCTCTACTGGACCGAC
ACGGGCACGGACCGCATCGAGGTGACGCGCCTCAACGGCACCTCCCGCA
AGATCCTGGTGTCGGAGGACCTGGACGAGCCCCGAGCCATCGCACTGCA
CCCCGTGATGGGgtaagacgggc

..... 3211 nt .....

Exon 7 Coordinates: 527d12_Contig309G 11311-11482
ttcttctccagCCTCATGTACTGGACAGACTGGGGAGAGAACCCTAAAATCGAG
TGTGCCAACTTGGATGGGCAGGAGCGGCGTGTGCTGGTCAATGCCTCCC
TCGGGTGGCCCAACGGCCTGGCCCTGGACCTGCAGGAGGGGAAGCTCT
ACTGGGGAGACGCCAAGACAGACAAGATCGAGgtgaggctcctgtgg

...... 13445 nt .....

Exon 8 Coordinates: 527d12_Contig309G 24927-25143
ccgtcctgcagGTGATCAATGTTGATGGGACGAAGAGGCGGACCCTCCTGGAG
GACAAGCTCCCGCACATTTTCGGGTTCACGCTGCTGGGGGACTTCATCT
ACTGGACTGACTGGCAGCGCCGCAGCATCGAGCGGGTGCACAAGGTCAA
GGCCAGCCGGGACGTCATCATTGACCAGCTGCCCGACCTGATGGGGCTC
AAAGCTGTGAATGTGGCCAAGGTCGTCGgtgagtccggggggtc

....2826 nt ......

Exon 9 Coordinates: 527d12_Contig309G 27969-28256
gttcgcttccagGAACCAACCCGTGTGCGGACAGGAACGGGGGGTGCAGCCACC
TGTGCTTCTTCACACCCCACGCAACCCGGTGTGGCTGCCCCATCGGCCT
GGAGCTGCTGAGTGACATGAAGACCTGCATCGTGCCTGAGGCCTTCTTG
GTCTTCACCAGCAGAGCCGCCATCCACAGGATCTCCCTCGAGACCAATA
ACAACGACGTGGCCATCCCGCTCACGGGCGTCAAGGAGGCCTCAGCCCT
GGACTTTGATGTGTCCAACAACCACATCTACTGGACAGACGTCAGCCTG
AAGgtagcgtgggc

......3102.....

FIG. 3B

Exon 10 Coordinates: 527d12_Contig309G 31358-31582
cctgctgccagACCATCAGCCGCGCCTTCATGAACGGGAGCTCGGTGGAGCAC
GTGGTGGAGTTTGGCCTTGACTACCCCGAGGGCATGGCCGTTGACTGGA
TGGGCAAGAACCTCTACTGGGCCGACACTGGGACCAACAGAATCGAAGT
GGCGCGGCTGGACGGGCAGTTCCGGCAAGTCCTCGTGTGGAGGGACTT
GGACAACCCGAGGTCGCTGGCCCTGGATCCCACCAAGGGgtaagtgtttgcctgtc

......1297 nt......

Exon 11 Coordinates: 527d12_Contig309G 32879-33064
gtgccttccagCTACATCTACTGGACCGAGTGGGGCGGCAAGCCGAGGATCGT
GCGGGCCTTCATGGACGGGACCAACTGCATGACGCTGGTGGACAAGGTG
GGCCGGGCCAACGACCTCACCATTGACTACGCTGACCAGCGCCTCTACT
GGACCGACCTGGACACCAACATGATCGAGTCGTCCAACATGCTGGgtgaggg
ccgggct

.......2069 nt.....

Exon 12 Coordinates: 527d12_Contig309G 35133-35454
gtgttcatgcagGTCAGGAGCGGGTCGTGATTGCCGACGATCTCCCGCACCCGT
TCGGTCTGACGCAGTACAGCGATTATATCTACTGGACAGACTGGAATCT
GCACAGCATTGAGCGGGCCGACAAGACTAGCGGCCGGAACCGCACCCTC
ATCCAGGGCCACCTGGACTTCGTGATGGACATCCTGGTGTTCCACTCCT
CCCGCCAGGATGGCCTCAATGACTGTATGCACAACAACGGGCAGTGTGG
GCAGCTGTGCCTTGCCATCCCCGGCGGCCACCGCTGCGGCTGCGCCTCA
CACTACACCCTGGACCCCAGCAGCCGCAACTGCAGCCgtaagtgcctcatggt

.......2006 nt......

Exon 13 Coordinates: 527d12_Contig309G 37460-37659
gcctcctctaCGCCCACCACCTTCTTGCTGTTCAGCCAGAAATCTGCCATCAGT
CGGATGATCCCGGACGACCAGCACAGCCCGGATCTCATCCTGCCCCTGC
ATGGACTGAGGAACGTCAAAGCCATCGACTATGACCCACTGGACAAGTT
CATCTACTGGGTGGATGGGCGCCAGAACATCAAGCGAGCCAAGGACGAC
GGGACCCAGgcaggtgccctgtgg

......6965 nt......

FIG. 3C

Exon 14 Coordinates: 527d12_Contig309G 44624-44832
ctttgtcttacagCCCTTTGTTTTGACCTCTCTGAGCCAAGGCCAAAACCCAGACA
GGCAGCCCCACGACCTCAGCATCGACATCTACAGCCGGACACTGTTCTG
GACGTGCGAGGCCACCAATACCATCAACGTCCACAGGCTGAGCGGGGAA
GCCATGGGGGTGGTGCTGCGTGGGGACCGCGACAAGCCCAGGGCCATC
GTCGTCAACGCGGAGCGAGGgtaggaggccaac

......1404 nt.....

Exon 15 Coordinates: 527d12_Contig309G 46236-46427
ccaccctcccgcagGTACCTGTACTTCACCAACATGCAGGACCGGGCAGCCAAGA
TCGAACGCGCAGCCCTGGACGGCACCGAGCGCGAGGTCCTCTTCACCAC
CGGCCTCATCCGCCCTGTGGCCCTGGTGGTGGACAACACACTGGGCAAG
CTGTTCTGGGTGGACGCGGACCTGAAGCGCATTGAGAGCTGTGACCTGT
CAGgtacgcgccccgg

.....686 nt.....

Exon 16 Coordinates: 527d12_Contig309G 47113-47322
ggctgcttgcagGGGCCAACCGCCTGACCCTGGAGGACGCCAACATCGTGCAGC
CTCTGGGCCTGACCATCCTTGGCAAGCATCTCTACTGGATCGACCGCCA
GCAGCAGATGATCGAGCGTGTGGAGAAGACCACCGGGGACAAGCGGAC
TCGCATCCAGGGCCGTGTCGCCCACCTCACTGGCATCCATGCAGTGGAG
GAAGTCAGCCTGGAGGAGTTCTgtacgtgggggc

.....3884 nt......

Exon 17 Coordinates: 527d12_Contig309G 51206-51331
ttgtctttgcagCAGCCCACCCATGTGCCCGTGACAATGGTGGCTGCTCCCACAT
CTGTATTGCCAAGGGTGATGGGACACCACGGTGCTCATGCCCAGTCCAC
CTCGTGCTCCTGCAGAACCTGCTGACCTGTGGAGgtaggtgtgacctaggtgc

....3905 nt.......

Exon 18 Coordinates: 527d12_Contig309G 55236-55472
gttctcctctgtccctcccccagAGCCGCCCACCTGCTCCCCGGACCAGTTTGCATGTG
CCACAGGGGAGATCGACTGTATCCCCGGGGCCTGGCGCTGTGACGGCTT
TCCCGAGTGCGATGACCAGAGCGACGAGGAGGGCTGCCCCGTGTGCTCC
GCCGCCCAGTTCCCCTGCGCGCGGGGTCAGTGTGTGGACCTGCGCCTGC
GCTGCGACGGCGAGGCAGACTGTCAGGACCGCTCAGACGAGGTGGACT
GTGACGgtgaggccctcc

.......3052 nt.....

FIG. 3D

Exon 19 Coordinates: 527d12_Contig309G 58524-58634
tctccttgcagCCATCTGCCTGCCCAACCAGTTCCGGTGTGCGAGCGGCCAGTG
TGTCCTCATCAAACAGCAGTGCGACTCCTTCCCCGACTGTATCGACGGCT
CCGACGAGCTCATGTGTGgtgagccagctt

........1448 nt......

Exon 20 Coordinates: 527d12_Contig309G 60082-60319
gtttgtctctggcagAAATCACCAAGCCGCCCTCAGACGACAGCCCGGCCCACAGC
AGTGCCATCGGGCCCGTCATTGGCATCATCCTCTCTCTCTTCGTCATGGG
TGGTGTCTATTTTGTGTGCCAGCGCGTGGTGTGCCAGCGCTATGCGGGG
GCCAACGGGCCCTTCCCGCACGAGTATGTCAGCGGGACCCCGCACGTGC
CCCTCAATTTCATAGCCCCGGGCGGTTCCCAGCATGGCCCCTTCACAGgta
aggagcctgagatatggaa

....1095 nt.....

Exon 21 Coordinates: 527d12_Contig309G 61414-61552
cttccctgccagGCATCGCATGCGGAAAGTCCATGATGAGCTCCGTGAGCCTGA
TGGGGGGCCGGGGCGGGGTGCCCCTCTACGACCGGAACCACGTCACAG
GGGCCTCGTCCAGCAGCTCGTCCAGCACGAAGGCCACGCTGTACCCGCC
Ggtgaggggcggg

......6513 nt......

Exon 22 Coordinates: 527d12_Contig309G 68065-68162
ttggctctcctcagATCCTGAACCCGCCGCCCTCCCCGGCCACGGACCCCTCCCT
GTACAACATGGACATGTTCTACTCTTCAAACATTCCGGCCACTGCGAGAC
CGTACAGgtaggacatcccctgcag

.......2273 nt.....

FIG. 3E

Exon 23 Coordinates: 527d12_Contig309G 70435-70901
tcaaacattccggccactgcgagaccgtacag**GCCCTACATCATTCGAGGAATGGCGCCCCC**
GACGACGCCCTGCAGCACCGACGTGTGTGACAGCGACTACAGCGCCAGC
CGCTGGAAGGCCAGCAAGTACTACCTGGATTTGAACTCGGACTCAGACC
CCTATCCACCCCCACCCACGCCCCACAGCCAGTACCTGTCGGCGGAGGA
CAGCTGCCCGCCCTCGCCCGCCACCGAGAGGAGCTACTTCCATCTCTTC
CCGCCCCCTCCGTCCCCCTGCACGGACTCATCCTGACCTCGGCCGGGCCA
CTCTGGCTTCTCTGTGCCCCTGTAAATAGTTTTAAATATGAACAAAGAAAAAA
ATATATTTTATGATTTAAAAAATAAATATAATTGGGATTTTAAAAACATGAGA
AATGTGAACTGTGATGGGGTGGGCAGGGCTGGGAGAACTTTGTACAGTGGAG
AAATATTTATAAACTTAATTTTGTAAAACA

FIG. 3F

Model for a LDL Receptor-Related protein, Zmax1

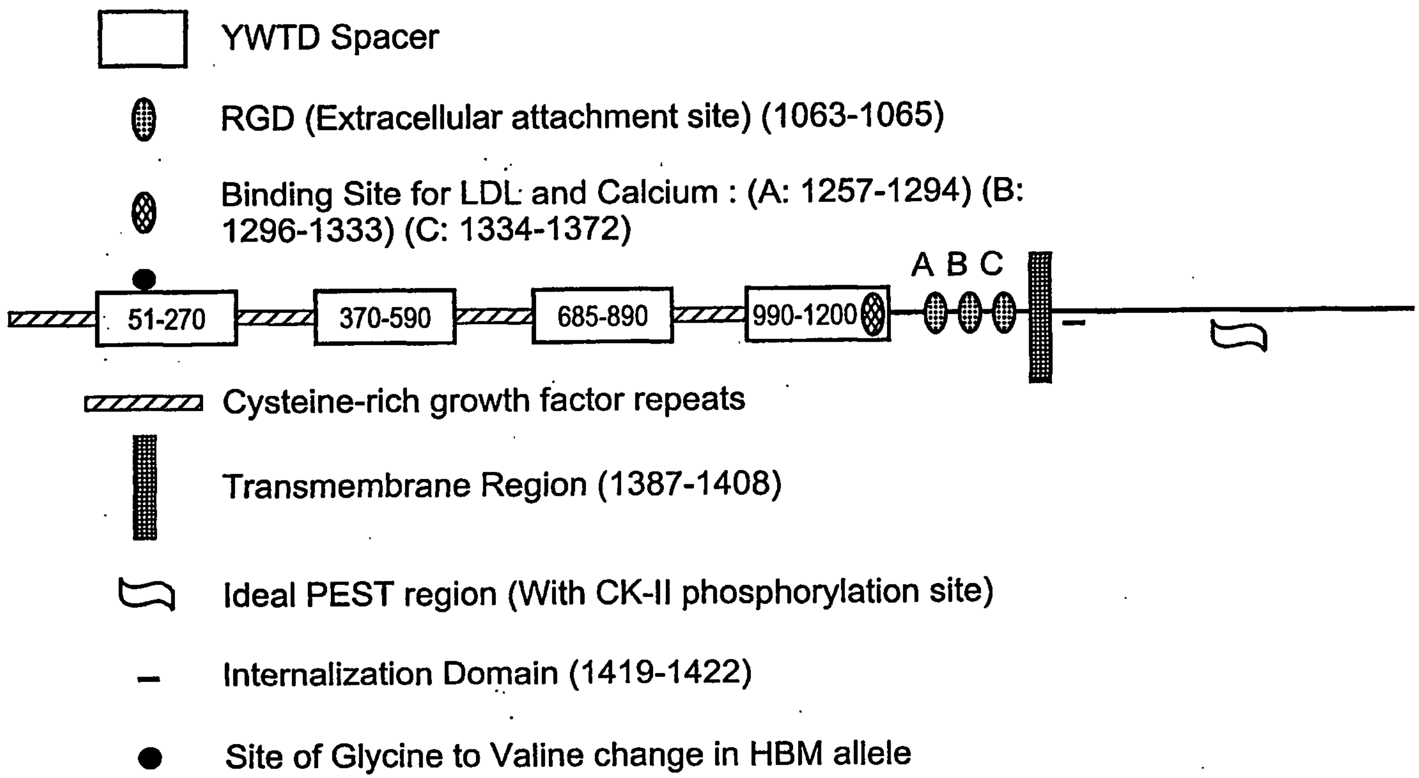


FIG. 4

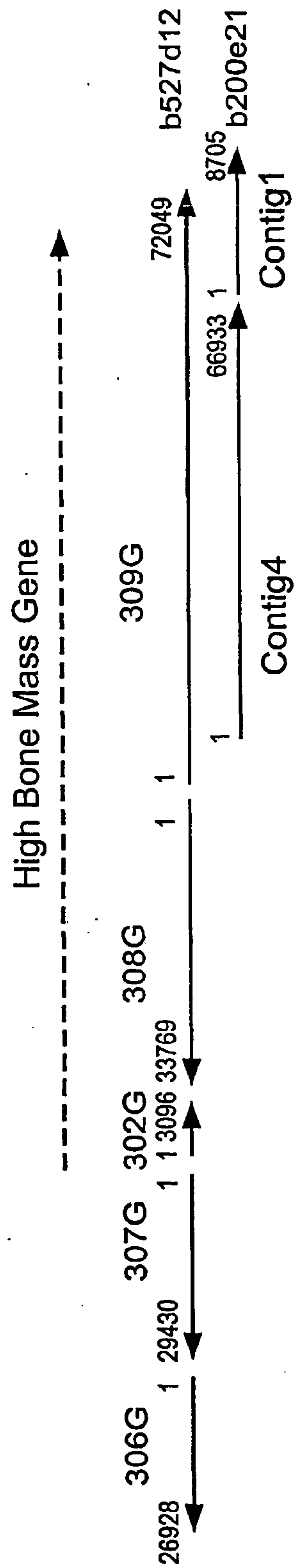

High Bone Mass Gene
b527d12
b200e21
72049
8705
Contig1
66933
1
309G
Contig4
1
1
1
1
308G
33769
3096
302G
1
1
307G
29430
1
306G
26928

FIG. 5

FIG. 6A

```
  1  ACTAAAGCGCCGCCGCCGCGCCATGGAGCCCGAGTGAGCGCGGCGCGGGCCCGTCCGGCC   60
 61  GCCGGACAACATGGAGGCAGCGCCGCCCGGGCCGCCGTGGCCGCTGCTGCTGCTGCTGCT  120
  1            M  E  A  A  P  P  G  P  P  W  P  L  L  L  L  L  L   17

121  GCTGCTGCTGGCGCTGTGCGGCTGCCCGGCCCCCGCCGCGGCCTCGCCGCTCCTGCTATT  180
 18   L  L  L  A  L  C  G  C  P  A  P  A  A  A  S  P  L  L  L  F   37

181  TGCCAACCGCCGGGACGTACGGCTGGTGGACGCCGGCGGAGTCAAGCTGGAGTCCACCAT  240
 38   A  N  R  R  D  V  R  L  V  D  A  G  G  V  K  L  E  S  T  I   57

241  CGTGGTCAGCGGCCTGGAGGATGCGGCCGCAGTGGACTTCCAGTTTTCCAAGGGAGCCGT  300
 58   V  V  S  G  L  E  D  A  A  A  V  D  F  Q  F  S  K  G  A  V   77

301  GTACTGGACAGACGTGAGCGAGGAGGCCATCAAGCAGACCTACCTGAACCAGACGGGGGC  360
 78   Y  W  T  D  V  S  E  E  A  I  K  Q  T  Y  L  N  Q  T  G  A   97

361  CGCCGTGCAGAACGTGGTCATCTCCGGCCTGGTCTCTCCCGACGGCCTCGCCTGCGACTG  420
 98   A  V  Q  N  V  V  I  S  G  L  V  S  P  D  G  L  A  C  D  W  117

421  GGTGGGCAAGAAGCTGTACTGGACGGACTCAGAGACCAACCGCATCGAGGTGGCCAACCT  480
118   V  G  K  K  L  Y  W  T  D  S  E  T  N  R  I  E  V  A  N  L  137

481  CAATGGCACATCCCGGAAGGTGCTCTTCTGGCAGGACCTTGACCAGCCGAGGGCCATCGC  540
138   N  G  T  S  R  K  V  L  F  W  Q  D  L  D  Q  P  R  A  I  A  157

541  CTTGGACCCCGCTCACGGGTACATGTACTGGACAGACTGGGGTGAGACGCCCCGGATTGA  600
158   L  D  P  A  H  G  Y  M  Y  W  T  D  W  G  E  T  P  R  I  E  177
```

FIG. 6B

```
601  GCGGGCAGGGATGGATGGCAGCACCCGGAAGATCATTGTGGACTCGGACATTTACTGGCC  660
178   R  A  G  M  D  G  S  T  R  K  I  I  V  D  S  D  I  Y  W  P   197

661  CAATGGACTGACCATCGACCTGGAGGAGCAGAAGCTCTACTGGGCTGACGCCAAGCTCAG  720
198   N  G  L  T  I  D  L  E  E  Q  K  L  Y  W  A  D  A  K  L  S   217

721  CTTCATCCACCGTGCCAACCTGGACGGCTCGTTCCGGCAGAAGGTGGTGGAGGGCAGCCT  780
218   F  I  H  R  A  N  L  D  G  S  F  R  Q  K  V  V  E  G  S  L   237

781  GACGCACCCCTTCGCCCTGACGCTCTCCGGGGACACTCTGTACTGGACAGACTGGCAGAC  840
238   T  H  P  F  A  L  T  L  S  G  D  T  L  Y  W  T  D  W  Q  T   257

841  CCGCTCCATCCATGCCTGCAACAAGCGCACTGGGGGGAAGAGGAAGGAGATCCTGAGTGC  900
258   R  S  I  H  A  C  N  K  R  T  G  G  K  R  K  E  I  L  S  A   277

901  CCTCTACTCACCCATGGACATCCAGGTGCTGAGCCAGGAGCGGCAGCCTTTCTTCCACAC  960
278   L  Y  S  P  M  D  I  Q  V  L  S  Q  E  R  Q  P  F  F  H  T   297

961  TCGCTGTGAGGAGGACAATGGCGGCTGCTCCCACCTGTGCCTGCTGTCCCCAAGCGAGCC  1020
298   R  C  E  E  D  N  G  G  C  S  H  L  C  L  L  S  P  S  E  P   317

1021 TTTCTACACATGCGCCTGCCCCACGGGTGTGCAGCTGCAGGACAACGGCAGGACGTGTAA  1080
318   F  Y  T  C  A  C  P  T  G  V  Q  L  Q  D  N  G  R  T  C  K   337

1081 GGCAGGAGCCGAGGAGGTGCTGCTGCTGGCCCGGCGGACGGACCTACGGAGGATCTCGCT  1140
338   A  G  A  E  E  V  L  L  L  A  R  R  T  D  L  R  R  I  S  L   357
```

FIG. 6C

```
1141  GGACACGCCGGACTTCACCGACATCGTGCTGCAGGTGGACGACATCCGGCACGCCATTGC  1200
 358   D  T  P  D  F  T  D  I  V  L  Q  V  D  D  I  R  H  A  I  A   377

1201  CATCGACTACGACCCGCTAGAGGGCTATGTCTACTGGACAGATGACGAGGTGCGGGCCAT  1260
 378   I  D  Y  D  P  L  E  G  Y  V  Y  W  T  D  D  E  V  R  A  I   397

1261  CCGCAGGGCGTACCTGGACGGGTCTGGGGCGCAGACGCTGGTCAACACCGAGATCAACGA  1320
 398   R  R  A  Y  L  D  G  S  G  A  Q  T  L  V  N  T  E  I  N  D   417

1321  CCCCGATGGCATCGCGGTCGACTGGGTGGCCCGAAACCTCTACTGGACCGACACGGGCAC  1380
 418   P  D  G  I  A  V  D  W  V  A  R  N  L  Y  W  T  D  T  G  T   437

1381  GGACCGCATCGAGGTGACGCGCCTCAACGGCACCTCCCGCAAGATCCTGGTGTCGGAGGA  1440
 438   D  R  I  E  V  T  R  L  N  G  T  S  R  K  I  L  V  S  E  D   457

1441  CCTGGACGAGCCCCGAGCCATCGCACTGCACCCCGTGATGGGCCTCATGTACTGGACAGA  1500
 458   L  D  E  P  R  A  I  A  L  H  P  V  M  G  L  M  Y  W  T  D   477

1501  CTGGGGAGAGAACCCTAAAATCGAGTGTGCCAACTTGGATGGGCAGGAGCGGCGTGTGCT  1560
 478   W  G  E  N  P  K  I  E  C  A  N  L  D  G  Q  E  R  R  V  L   497

1561  GGTCAATGCCTCCCTCGGGTGGCCCAACGGCCTGGCCCTGGACCTGCAGGAGGGGAAGCT  1620
 498   V  N  A  S  L  G  W  P  N  G  L  A  L  D  L  Q  E  G  K  L   517

1621  CTACTGGGGAGACGCCAAGACAGACAAGATCGAGGTGATCAATGTTGATGGGACGAAGAG  1680
 518   Y  W  G  D  A  K  T  D  K  I  E  V  I  N  V  D  G  T  K  R   537
```

FIG. 6D

```
1681  GCGGACCCTCCTGGAGGACAAGCTCCCGCACATTTTCGGGTTCACGCTGCTGGGGGACTT  1740
 538   R  T  L  L  E  D  K  L  P  H  I  F  G  F  T  L  L  G  D  F   557

1741  CATCTACTGGACTGACTGGCAGCGCCGCAGCATCGAGCGGGTGCACAAGGTCAAGGCCAG  1800
 558   I  Y  W  T  D  W  Q  R  R  S  I  E  R  V  H  K  V  K  A  S   577

1801  CCGGGACGTCATCATTGACCAGCTGCCCGACCTGATGGGGCTCAAAGCTGTGAATGTGGC  1860
 578   R  D  V  I  I  D  Q  L  P  D  L  M  G  L  K  A  V  N  V  A   597

1861  CAAGGTCGTCGGAACCAACCCGTGTGCGGACAGGAACGGGGGGTGCAGCCACCTGTGCTT  1920
 598   K  V  V  G  T  N  P  C  A  D  R  N  G  G  C  S  H  L  C  F   617

1921  CTTCACACCCCACGCAACCCGGTGTGGCTGCCCCATCGGCCTGGAGCTGCTGAGTGACAT  1980
 618   F  T  P  H  A  T  R  C  G  C  P  I  G  L  E  L  L  S  D  M   637

1981  GAAGACCTGCATCGTGCCTGAGGCCTTCTTGGTCTTCACCAGCAGAGCCGCCATCCACAG  2040
 638   K  T  C  I  V  P  E  A  F  L  V  F  T  S  R  A  A  I  H  R   657

2041  GATCTCCCTCGAGACCAATAACAACGACGTGGCCATCCCGCTCACGGGCGTCAAGGAGGC  2100
 658   I  S  L  E  T  N  N  N  D  V  A  I  P  L  T  G  V  K  E  A   677

2101  CTCAGCCCTGGACTTTGATGTGTCCAACAACCACATCTACTGGACAGACGTCAGCCTGAA  2160
 678   S  A  L  D  F  D  V  S  N  N  H  I  Y  W  T  D  V  S  L  K   697

2161  GACCATCAGCCGCGCCTTCATGAACGGGAGCTCGGTGGAGCACGTGGTGGAGTTTGGCCT  2220
 698   T  I  S  R  A  F  M  N  G  S  S  V  E  H  V  V  E  F  G  L   717
```

FIG. 6E

```
2221  TGACTACCCCGAGGGCATGGCCGTTGACTGGATGGGCAAGAACCTCTACTGGGCCGACAC  2280
 718   D  Y  P  E  G  M  A  V  D  W  M  G  K  N  L  Y  W  A  D  T    737

2281  TGGGACCAACAGAATCGAAGTGGCGCGGCTGGACGGGCAGTTCCGGCAAGTCCTCGTGTG  2340
 738   G  T  N  R  I  E  V  A  R  L  D  G  Q  F  R  Q  V  L  V  W    757

2341  GAGGGACTTGGACAACCCGAGGTCGCTGGCCCTGGATCCCACCAAGGGCTACATCTACTG  2400
 758   R  D  L  D  N  P  R  S  L  A  L  D  P  T  K  G  Y  I  Y  W    777

2401  GACCGAGTGGGGCGGCAAGCCGAGGATCGTGCGGGCCTTCATGGACGGGACCAACTGCAT  2460
 778   T  E  W  G  G  K  P  R  I  V  R  A  F  M  D  G  T  N  C  M    797

2461  GACGCTGGTGGACAAGGTGGGCCGGGCCAACGACCTCACCATTGACTACGCTGACCAGCG  2520
 798   T  L  V  D  K  V  G  R  A  N  D  L  T  I  D  Y  A  D  Q  R    817

2521  CCTCTACTGGACCGACCTGGACACCAACATGATCGAGTCGTCCAACATGCTGGGTCAGGA  2580
 818   L  Y  W  T  D  L  D  T  N  M  I  E  S  S  N  M  L  G  Q  E    837

2581  GCGGGTCGTGATTGCCGACGATCTCCCGCACCCGTTCGGTCTGACGCAGTACAGCGATTA  2640
 838   R  V  V  I  A  D  D  L  P  H  P  F  G  L  T  Q  Y  S  D  Y    857

2641  TATCTACTGGACAGACTGGAATCTGCACAGCATTGAGCGGGCCGACAAGACTAGCGGCCG  2700
 858   I  Y  W  T  D  W  N  L  H  S  I  E  R  A  D  K  T  S  G  R    877

2701  GAACCGCACCCTCATCCAGGGCCACCTGGACTTCGTGATGGACATCCTGGTGTTCCACTC  2760
 878   N  R  T  L  I  Q  G  H  L  D  F  V  M  D  I  L  V  F  H  S    897
```

FIG. 6F

```
2761 CTCCCGCCAGGATGGCCTCAATGACTGTATGCACAACAACGGGCAGTGTGGGCAGCTGTG 2820
 898  S  R  Q  D  G  L  N  D  C  M  H  N  N  G  Q  C  G  Q  L  C   917

2821 CCTTGCCATCCCCGGCGGCCACCGCTGCGGCTGCGCCTCACACTACACCCTGGACCCCAG 2880
 918  L  A  I  P  G  G  H  R  C  G  C  A  S  H  Y  T  L  D  P  S   937

2881 CAGCCGCAACTGCAGCCCGCCCACCACCTTCTTGCTGTTCAGCCAGAAATCTGCCATCAG 2940
 938  S  R  N  C  S  P  P  T  T  F  L  L  F  S  Q  K  S  A  I  S   957

2941 TCGGATGATCCCGGACGACCAGCACAGCCCGGATCTCATCCTGCCCCTGCATGGACTGAG 3000
 958  R  M  I  P  D  D  Q  H  S  P  D  L  I  L  P  L  H  G  L  R   977

3001 GAACGTCAAAGCCATCGACTATGACCCACTGGACAAGTTCATCTACTGGGTGGATGGGCG 3060
 978  N  V  K  A  I  D  Y  D  P  L  D  K  F  I  Y  W  V  D  G  R   997

3061 CCAGAACATCAAGCGAGCCAAGGACGACGGGACCCAGCCCTTTGTTTTGACCTCTCTGAG 3120
 998  Q  N  I  K  R  A  K  D  D  G  T  Q  P  F  V  L  T  S  L  S  1017

3121 CCAAGGCCAAAACCCAGACAGGCAGCCCCACGACCTCAGCATCGACATCTACAGCCGGAC 3180
1018  Q  G  Q  N  P  D  R  Q  P  H  D  L  S  I  D  I  Y  S  R  T  1037

3181 ACTGTTCTGGACGTGCGAGGCCACCAATACCATCAACGTCCACAGGCTGAGCGGGGAAGC 3240
1038  L  F  W  T  C  E  A  T  N  T  I  N  V  H  R  L  S  G  E  A  1057

3241 CATGGGGGTGGTGCTGCGTGGGGACCGCGACAAGCCCAGGGCCATCGTCGTCAACGCGGA 3300
1058  M  G  V  V  L  R  G  D  R  D  K  P  R  A  I  V  V  N  A  E  1077
```

FIG. 6G

```
3301  GCGAGGGTACCTGTACTTCACCAACATGCAGGACCGGGCAGCCAAGATCGAACGCGCAGC  3360
1078   R  G  Y  L  Y  F  T  N  M  Q  D  R  A  A  K  I  E  R  A  A   1097

3361  CCTGGACGGCACCGAGCGCGAGGTCCTCTTCACCACCGGCCTCATCCGCCCTGTGGCCCT  3420
1098   L  D  G  T  E  R  E  V  L  F  T  T  G  L  I  R  P  V  A  L   1117

3421  GGTGGTGGACAACACACTGGGCAAGCTGTTCTGGGTGGACGCGGACCTGAAGCGCATTGA  3480
1118   V  V  D  N  T  L  G  K  L  F  W  V  D  A  D  L  K  R  I  E   1137

3481  GAGCTGTGACCTGTCAGGGGCCAACCGCCTGACCCTGGAGGACGCCAACATCGTGCAGCC  3540
1138   S  C  D  L  S  G  A  N  R  L  T  L  E  D  A  N  I  V  Q  P   1157

3541  TCTGGGCCTGACCATCCTTGGCAAGCATCTCTACTGGATCGACCGCCAGCAGCAGATGAT  3600
1158   L  G  L  T  I  L  G  K  H  L  Y  W  I  D  R  Q  Q  Q  M  I   1177

3601  CGAGCGTGTGGAGAAGACCACCGGGGACAAGCGGACTCGCATCCAGGGCCGTGTCGCCCA  3660
1178   E  R  V  E  K  T  T  G  D  K  R  T  R  I  Q  G  R  V  A  H   1197

3661  CCTCACTGGCATCCATGCAGTGGAGGAAGTCAGCCTGGAGGAGTTCTCAGCCCACCCATG  3720
1198   L  T  G  I  H  A  V  E  E  V  S  L  E  E  F  S  A  H  P  C   1217

3721  TGCCCGTGACAATGGTGGCTGCTCCCACATCTGTATTGCCAAGGGTGATGGGACACCACG  3780
1218   A  R  D  N  G  G  C  S  H  I  C  I  A  K  G  D  G  T  P  R   1237

3781  GTGCTCATGCCCAGTCCACCTCGTGCTCCTGCAGAACCTGCTGACCTGTGGAGAGCCGCC  3840
1238   C  S  C  P  V  H  L  V  L  L  Q  N  L  L  T  C  G  E  P  P   1257
```

FIG. 6H

```
3841  CACCTGCTCCCCGGACCAGTTTGCATGTGCCACAGGGGAGATCGACTGTATCCCCGGGGC  3900
1258   T  C  S  P  D  Q  F  A  C  A  T  G  E  I  D  C  I  P  G  A   1277

3901  CTGGCGCTGTGACGGCTTTCCCGAGTGCGATGACCAGAGCGACGAGGAGGGCTGCCCCGT  3960
1278   W  R  C  D  G  F  P  E  C  D  D  Q  S  D  E  E  G  C  P  V   1297

3961  GTGCTCCGCCGCCCAGTTCCCCTGCGCGCGGGGTCAGTGTGTGGACCTGCGCCTGCGCTG  4020
1298   C  S  A  A  Q  F  P  C  A  R  G  Q  C  V  D  L  R  L  R  C   1317

4021  CGACGGCGAGGCAGACTGTCAGGACCGCTCAGACGAGGTGGACTGTGACGCCATCTGCCT  4080
1318   D  G  E  A  D  C  Q  D  R  S  D  E  V  D  C  D  A  I  C  L   1337

4081  GCCCAACCAGTTCCGGTGTGCGAGCGGCCAGTGTGTCCTCATCAAACAGCAGTGCGACTC  4140
1338   P  N  Q  F  R  C  A  S  G  Q  C  V  L  I  K  Q  Q  C  D  S   1357

4141  CTTCCCCGACTGTATCGACGGCTCCGACGAGCTCATGTGTGAAATCACCAAGCCGCCCTC  4200
1358   F  P  D  C  I  D  G  S  D  E  L  M  C  E  I  T  K  P  P  S   1377

4201  AGACGACAGCCCGGCCCACAGCAGTGCCATCGGGCCCGTCATTGGCATCATCCTCTCTCT  4260
1378   D  D  S  P  A  H  S  S  A  I  G  P  V  I  G  I  I  L  S  L   1397

4261  CTTCGTCATGGGTGGTGTCTATTTTGTGTGCCAGCGCGTGGTGTGCCAGCGCTATGCGGG  4320
1398   F  V  M  G  G  V  Y  F  V  C  Q  R  V  V  C  Q  R  Y  A  G   1417

4321  GGCCAACGGGCCCTTCCCGCACGAGTATGTCAGCGGGACCCCGCACGTGCCCCTCAATTT  4380
1418   A  N  G  P  F  P  H  E  Y  V  S  G  T  P  H  V  P  L  N  F   1437
```

FIG. 6I

```
4381 CATAGCCCCGGGCGGTTCCCAGCATGGCCCCTTCACAGGCATCGCATGCGGAAAGTCCAT 4440
1438  I  A  P  G  G  S  Q  H  G  P  F  T  G  I  A  C  G  K  S  M  1457

4441 GATGAGCTCCGTGAGCCTGATGGGGGGCCGGGGCGGGGTGCCCCTCTACGACCGGAACCA 4500
1458  M  S  S  V  S  L  M  G  G  R  G  G  V  P  L  Y  D  R  N  H  1477

4501 CGTCACAGGGGCCTCGTCCAGCAGCTCGTCCAGCACGAAGGCCACGCTGTACCCGCCGAT 4560
1478  V  T  G  A  S  S  S  S  S  S  S  T  K  A  T  L  Y  P  P  I  1497

4561 CCTGAACCCGCCGCCCTCCCCGGCCACGGACCCCTCCCTGTACAACATGGACATGTTCTA 4620
1498  L  N  P  P  P  S  P  A  T  D  P  S  L  Y  N  M  D  M  F  Y  1517

4621 CTCTTCAAACATTCCGGCCACTGCGAGACCGTACAGGCCCTACATCATTCGAGGAATGGC 4680
1518  S  S  N  I  P  A  T  A  R  P  Y  R  P  Y  I  I  R  G  M  A  1537

4681 GCCCCCGACGACGCCCTGCAGCACCGACGTGTGTGACAGCGACTACAGCGCCAGCCGCTG 4740
1538  P  P  T  T  P  C  S  T  D  V  C  D  S  D  Y  S  A  S  R  W  1557

4741 GAAGGCCAGCAAGTACTACCTGGATTTGAACTCGGACTCAGACCCCTATCCACCCCCACC 4800
1558  K  A  S  K  Y  Y  L  D  L  N  S  D  S  D  P  Y  P  P  P  P  1577

4801 CACGCCCCACAGCCAGTACCTGTCGGCGGAGGACAGCTGCCCGCCCTCGCCCGCCACCGA 4860
1578  T  P  H  S  Q  Y  L  S  A  E  D  S  C  P  P  S  P  A  T  E  1597

4861 GAGGAGCTACTTCCATCTCTTCCCGCCCCCTCCGTCCCCCTGCACGGACTCATCCTGACC 4920
1598  R  S  Y  F  H  L  F  P  P  P  P  S  P  C  T  D  S  S        1615
```

FIG. 6J

```
4921   TCGGCCGGGCCACTCTGGCTTCTCTGTGCCCCTGTAAATAGTTTTAAATATGAACAAAGA   4980
4981   AAAAAATATATTTTATGATTTAAAAAATAAATATAATTGGATTTTAAAAACATGAGAAA    5040
5041   TGTGAACTGTGATGGGGTGGCAGGGCTGGGAGAACTTTGTACAGTGGAGAAATATTTAT    5100
5101   AAACTTAATTTTGTAAAACA   5120
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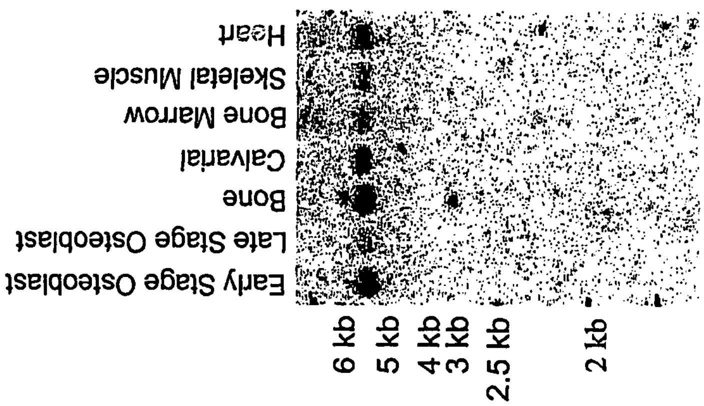
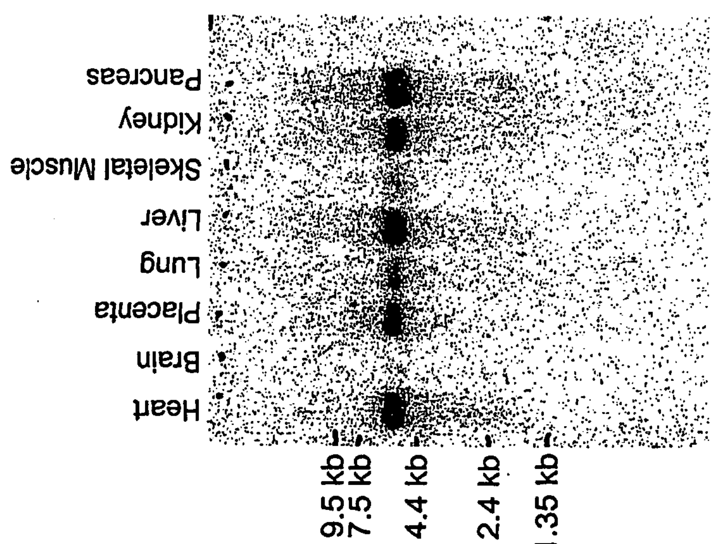


Northern Blot Analysis - Zmax 1

FIG. 7B



Northern Blot Analysis - Zmax 1

FIG. 7A

Zmax 1 random samples
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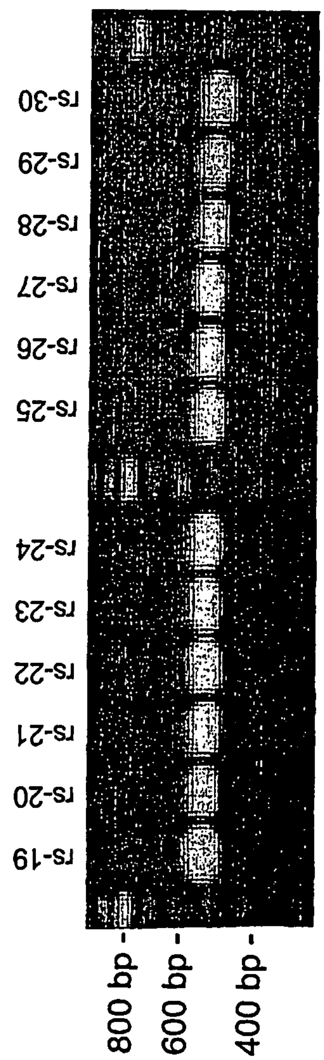
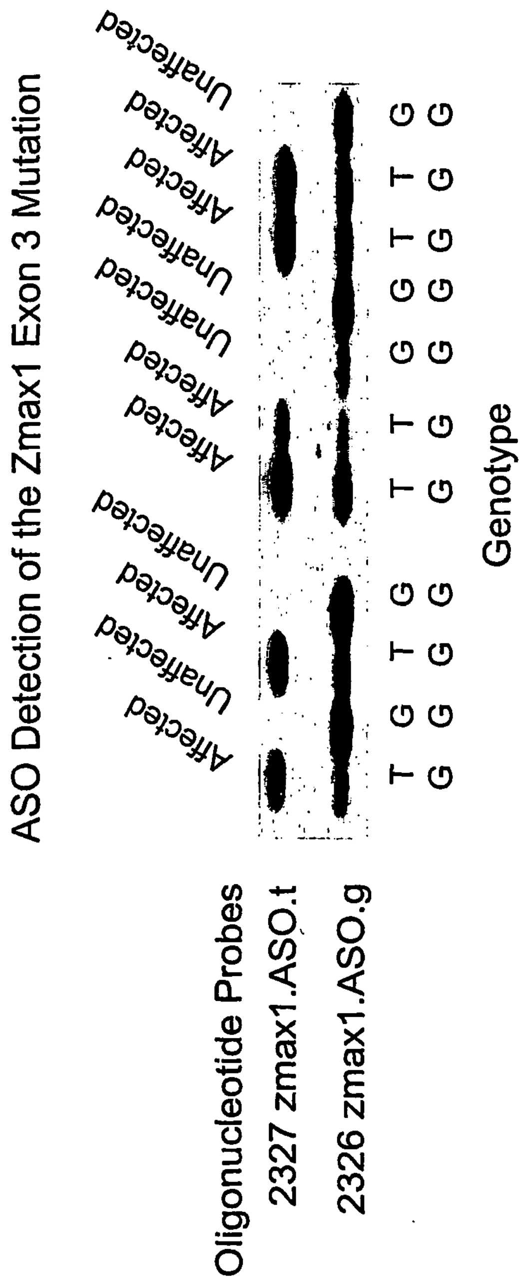


FIG. 8


ASO Detection of the Zmax1 Exon 3 Mutation
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Unaffected
Affected
Unaffected
Affected
Affected
Unaffected
Unaffected
Affected
Affected
Unaffected
Oligonucleotide Probes
2327 zmax1.ASO.t
2326 zmax1.ASO.g
T G T G T T G G T T G
G G G G G G G G G G G
Genotype

FIG. 9

Mouse Zmax1 In situ hybridization
100X Magnification

Antisense probe

FIG. 10A

Mouse Zmax1 In situ hybridization
100X Magnification

Sense probe

FIG. 10B

Mouse Zmax1 In situ hybridization
400X Magnification
Antisense probe

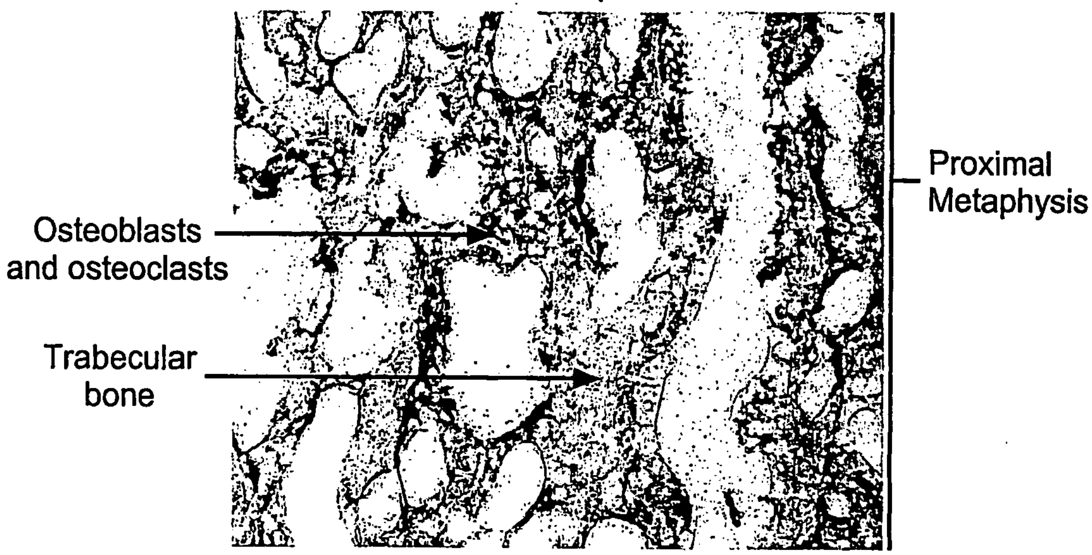


FIG. 11A

Mouse Zmax1 In situ hybridization
400X Magnification
Sense probe

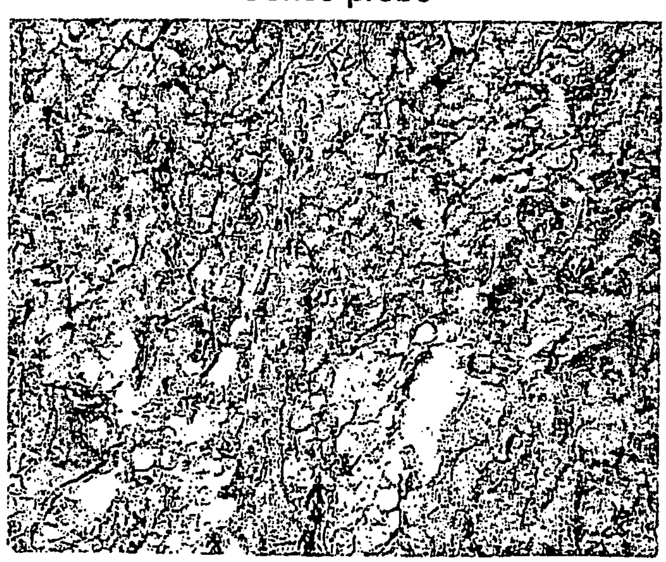


FIG. 11B

Mouse Zmax1 In situ hybridization
400X Magnification
Antisense probe

FIG. 12A

Mouse Zmax1 In situ hybridization
400X Magnification
Sense probe

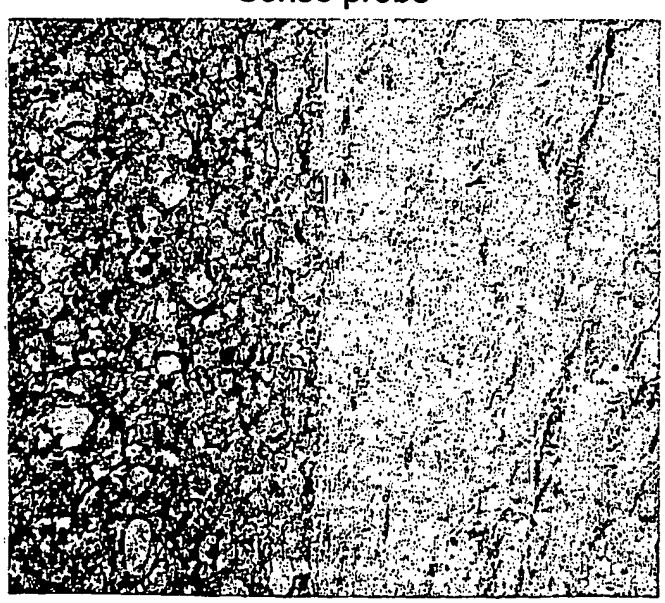
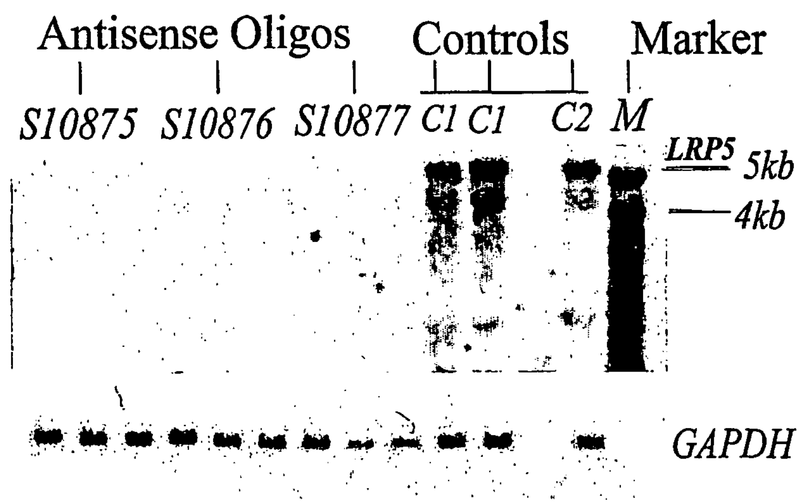


FIG. 12B

Antisense Inhibition of Zmax1 Expression



MC-3T3 cells

FIG. 13

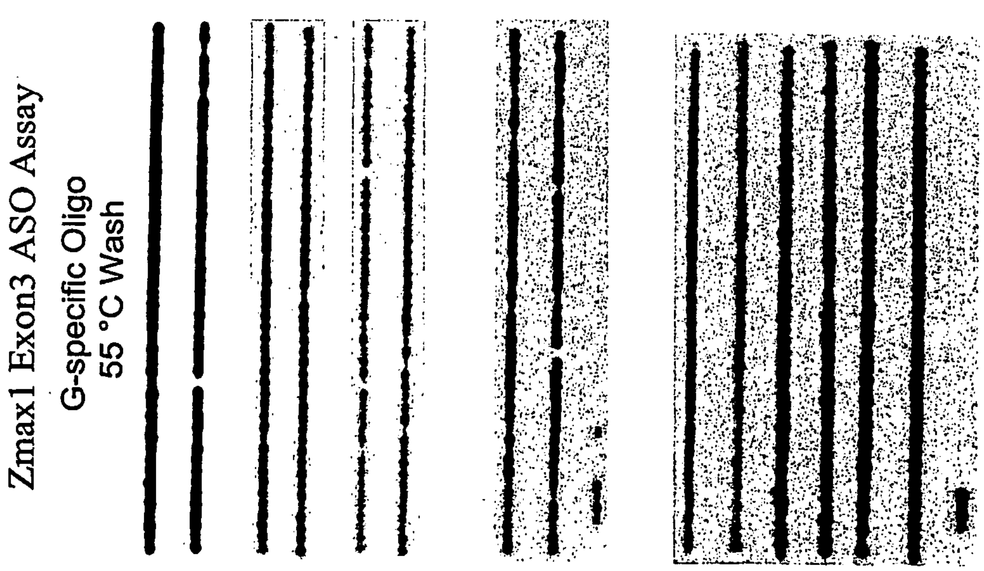


FIG. 14A

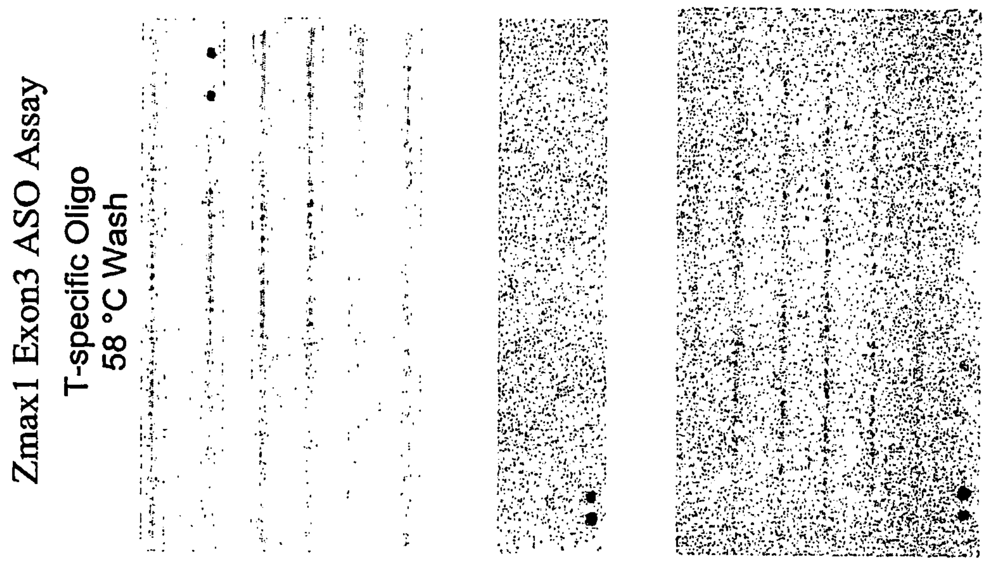


FIG. 14B

Possible Involvement of Zmax1 in Focal Adhesion Signaling

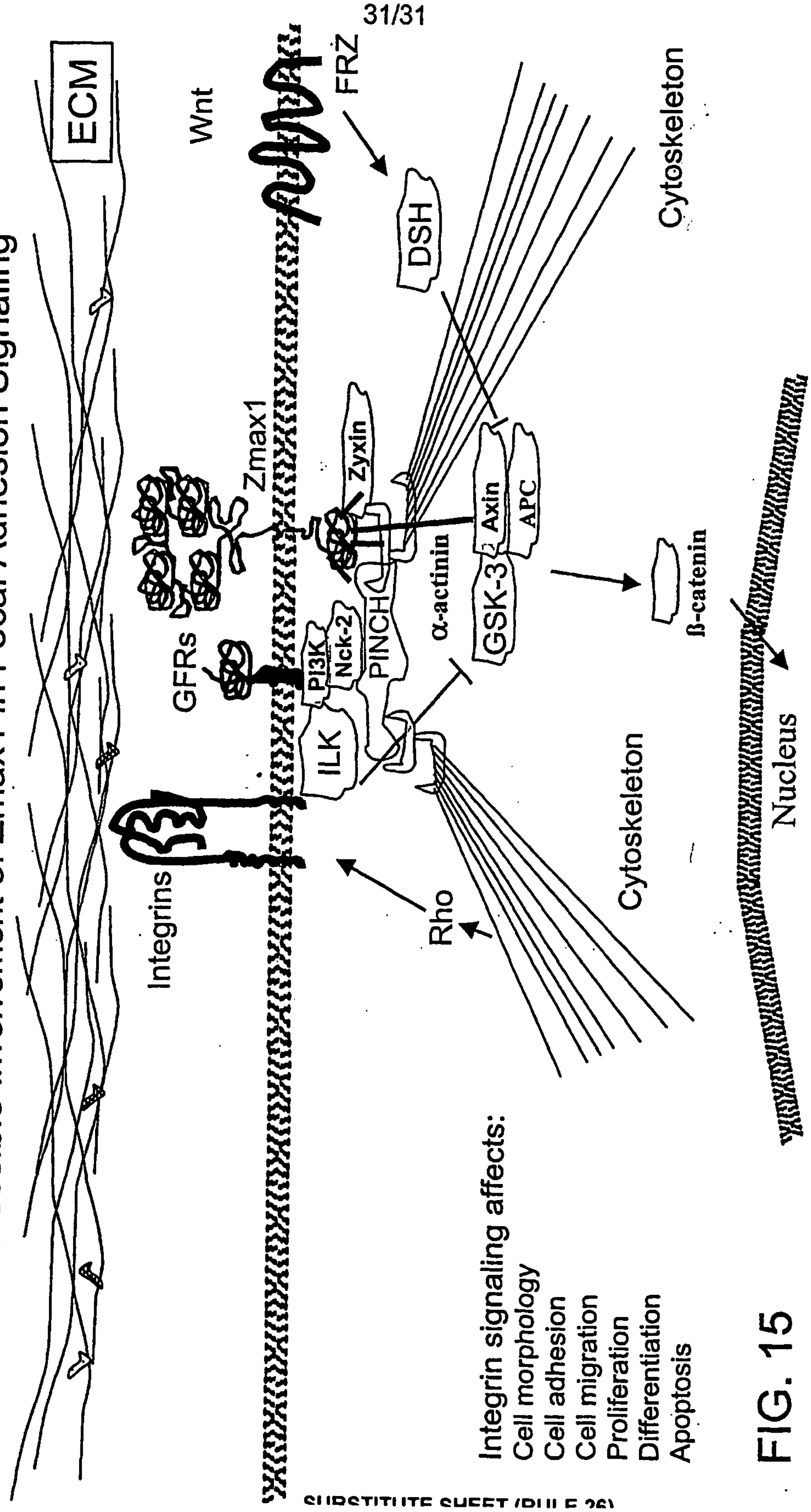


FIG. 15

SEQUENCE LISTING

<110> John P. Carulli et al.

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<150> US 09/544,398

<151> 2000-04-05

<150> US 09/543,771

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            Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu
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Leu Leu Leu Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala

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Ala Ala Ser Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu

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Val Asp Ala Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly

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Leu Glu Asp Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val

65 70 75

tac tgg aca gac gtg agc gag gag gcc atc aag cag acc tac ctg aac 349

Tyr Trp Thr Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn

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cag acg ggg gcc gcc gtg cag aac gtg gtc atc tcc ggc ctg gtc tct 397

Gln Thr Gly Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser

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ccc gac ggc ctc gcc tgc gac tgg gtg ggc aag aag ctg tac tgg acg 445

Pro Asp Gly Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr

110 115 120 125

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Asp Ser Glu Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser

130 135 140

cgg aag gtg ctc ttc tgg cag gac ctt gac cag ccg agg gcc atc gcc 541

Arg Lys Val Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala

145 150 155

ttg gac ccc gct cac ggg tac atg tac tgg aca gac tgg ggt gag acg 589

Leu Asp Pro Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr

160 165 170

ccc cgg att gag cgg gca ggg atg gat ggc agc acc cgg aag atc att 637

Pro Arg Ile Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile

175 180 185

gtg gac tcg gac att tac tgg ccc aat gga ctg acc atc gac ctg gag 685

Val Asp Ser Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu

190 195 200 205

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Glu Gln Lys Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg

210 215 220

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Ala Asn Leu Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu

225 230 235

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Thr His Pro Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr

240 245 250

gac tgg cag acc cgc tcc atc cat gcc tgc aac aag cgc act ggg ggg 877

Asp Trp Gln Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly

255 260 265

aag agg aag gag atc ctg agt gcc ctc tac tca ccc atg gac atc cag 925

Lys Arg Lys Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln

270 275 280 285

gtg ctg agc cag gag cgg cag cct ttc ttc cac act cgc tgt gag gag 973

Val Leu Ser Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu

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Asp Asn Gly Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro

305 310 315

ttc tac aca tgc gcc tgc ccc acg ggt gtg cag ctg cag gac aac ggc 1069

Phe Tyr Thr Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly

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Arg Thr Cys Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg

335 340 345

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Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile

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Val Leu Gln Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp

370 375 380

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Pro Leu Glu Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile

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400 405 410

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Glu Ile Asn Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn

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670 675 680 685

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690 695 700

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Thr Leu Val Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr

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Ser Ser Asn Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu

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Val Asp Ala Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly

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Tyr Trp Thr Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn

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Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile

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895 900 905

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gag cgc gag gtc ctc ttc acc acc ggc ctc atc cgc cct gtg gcc ctg 3421

Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg Pro Val Ala Leu

1105 1110 1115

gtg gtg gac aac aca ctg ggc aag ctg ttc tgg gtg gac gcg gac ctg 3469

Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp Val Asp Ala Asp Leu

1120 1125 1130

aag cgc att gag agc tgt gac ctg tca ggg gcc aac cgc ctg acc ctg 3517

Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala Asn Arg Leu Thr Leu

1135 1140 1145

gag gac gcc aac atc gtg cag cct ctg ggc ctg acc atc ctt ggc aag 3565

Glu Asp Ala Asn Ile Val Gln Pro Leu Gly Leu Thr Ile Leu Gly Lys

1150 1155 1160 1165

cat ctc tac tgg atc gac cgc cag cag cag atg atc gag cgt gtg gag 3613

His Leu Tyr Trp Ile Asp Arg Gln Gln Gln Met Ile Glu Arg Val Glu

1170 1175 1180

aag acc acc ggg gac aag cgg act cgc atc cag ggc cgt gtc gcc cac 3661

Lys Thr Thr Gly Asp Lys Arg Thr Arg Ile Gln Gly Arg Val Ala His

1185 1190 1195

ctc act ggc atc cat gca gtg gag gaa gtc agc ctg gag gag ttc tca 3709
Leu Thr Gly Ile His Ala Val Glu Glu Val Ser Leu Glu Glu Phe Ser
1200 1205 1210

gcc cac cca tgt gcc cgt gac aat ggt ggc tgc tcc cac atc tgt att 3757
Ala His Pro Cys Ala Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile
1215 1220 1225

gcc aag ggt gat ggg aca cca cgg tgc tca tgc cca gtc cac ctc gtg 3805
Ala Lys Gly Asp Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val
1230 1235 1240 1245

ctc ctg cag aac ctg ctg acc tgt gga gag ccg ccc acc tgc tcc ccg 3853
Leu Leu Gln Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro
1250 1255 1260

gac cag ttt gca tgt gcc aca ggg gag atc gac tgt atc ccc ggg gcc 3901
Asp Gln Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala
1265 1270 1275

tgg cgc tgt gac ggc ttt ccc gag tgc gat gac cag agc gac gag gag 3949
Trp Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu
1280 1285 1290

ggc tgc ccc gtg tgc tcc gcc gcc cag ttc ccc tgc gcg cgg ggt cag 3997
Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly Gln
1295 1300 1305

tgt gtg gac ctg cgc ctg cgc tgc gac ggc gag gca gac tgt cag gac 4045
Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln Asp
1310 1315 1320 1325

cgc tca gac gag gtg gac tgt gac gcc atc tgc ctg ccc aac cag ttc 4093
Arg Ser Asp Glu Val Asp Cys Asp Ala Ile Cys Leu Pro Asn Gln Phe
1330 1335 1340

cgg tgt gcg agc ggc cag tgt gtc ctc atc aaa cag cag tgc gac tcc 4141
Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln Gln Cys Asp Ser
1345 1350 1355

ttc ccc gac tgt atc gac ggc tcc gac gag ctc atg tgt gaa atc acc 4189
Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu Met Cys Glu Ile Thr
1360 1365 1370

aag ccg ccc tca gac gac agc ccg gcc cac agc agt gcc atc ggg ccc 4237
Lys Pro Pro Ser Asp Asp Ser Pro Ala His Ser Ser Ala Ile Gly Pro
1375 1380 1385

gtc att ggc atc atc ctc tct ctc ttc gtc atg ggt ggt gtc tat ttt 4285
Val Ile Gly Ile Ile Leu Ser Leu Phe Val Met Gly Gly Val Tyr Phe
1390 1395 1400 1405

gtg tgc cag cgc gtg gtg tgc cag cgc tat gcg ggg gcc aac ggg ccc 4333
Val Cys Gln Arg Val Val Cys Gln Arg Tyr Ala Gly Ala Asn Gly Pro
1410 1415 1420

ttc ccg cac gag tat gtc agc ggg acc ccg cac gtg ccc ctc aat ttc 4381
Phe Pro His Glu Tyr Val Ser Gly Thr Pro His Val Pro Leu Asn Phe
1425 1430 1435

ata gcc ccg ggc ggt tcc cag cat ggc ccc ttc aca ggc atc gca tgc 4429
Ile Ala Pro Gly Gly Ser Gln His Gly Pro Phe Thr Gly Ile Ala Cys
1440 1445 1450

gga aag tcc atg atg agc tcc gtg agc ctg atg ggg ggc cgg ggc ggg 4477
Gly Lys Ser Met Met Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly
1455 1460 1465

gtg ccc ctc tac gac cgg aac cac gtc aca ggg gcc tcg tcc agc agc 4525
Val Pro Leu Tyr Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser
1470 1475 1480 1485

tcg tcc agc acg aag gcc acg ctg tac ccg ccg atc ctg aac ccg ccg 4573

Ser Ser Ser Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro

1490 1495 1500

ccc tcc ccg gcc acg gac ccc tcc ctg tac aac atg gac atg ttc tac 4621

Pro Ser Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr

1505 1510 1515

tct tca aac att ccg gcc act gcg aga ccg tac agg ccc tac atc att 4669

Ser Ser Asn Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Ile Ile

1520 1525 1530

cga gga atg gcg ccc ccg acg acg ccc tgc agc acc gac gtg tgt gac 4717

Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp

1535 1540 1545

agc gac tac agc gcc agc cgc tgg aag gcc agc aag tac tac ctg gat 4765

Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp

1550 1555 1560 1565

ttg aac tcg gac tca gac ccc tat cca ccc cca ccc acg ccc cac agc 4813

Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His Ser

1570 1575 1580

cag tac ctg tcg gcg gag gac agc tgc ccg ccc tcg ccc gcc acc gag 4861

Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro Ala Thr Glu

1585 1590 1595

agg agc tac ttc cat ctc ttc ccg ccc cct ccg tcc ccc tgc acg gac 4909

Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro Ser Pro Cys Thr Asp

1600 1605 1610

tca tcc tgacctcggc cgggccactc tggcttctct gtgcccctgt aaatagtttt 4965

Ser Ser

1615

aaatatgaac aaagaaaaaa atatatttta tgatttaaaa aataaatata attgggattt 5025

taaaaacatg agaaatgtga actgtgatgg ggtgggcagg gctgggagaa ctttgtacag 5085

tggagaaata tttataaact taattttgta aaaca 5120

<210> 3

<211> 1615

<212> PRT

<213> Homo sapiens

<400> 3

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Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
            20   25   30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
        35   40   45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
    50   55   60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65   70   75   80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
                85   90   95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
            100   105   110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
        115   120   125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val

130 135 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Lys Ala Ile Ala Leu Asp Pro

145 150 155 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile

165 170 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser

180 185 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys

195 200 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu

210 215 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro

225 230 235 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln

245 250 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys

260 265 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser

275 280 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly

290 295 300

Gly Trp Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr

305 310 315 320

Cys Ala Cys Pro Thr Gly Val Gln Met Gln Asp Asn Gly Arg Thr Cys

325 330 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu

340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln

355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu

370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala

385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn

405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp

420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr

435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile

450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu

465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val

485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu

500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu

515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys

530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp

545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala

565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys

580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg

595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg

610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys

625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His

645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr

660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His

675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Asn Ile Ser Arg Ala Phe Met

690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro

705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp

725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg

740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu

755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro

770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val

785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln

805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn

820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro

835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn

850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr

865 870 875 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His

885 890 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln

900 905 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys

915 920 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro

930 935 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile

945 950 955 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu

965 970 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr

980 985 990

Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr

995 1000 1005

Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp Arg

1010 1015 1020

Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe Trp

1025 1030 1035 1040

Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Ser Gly Glu

1045 1050 1055

Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro Arg Ala Ile

1060 1065 1070

Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe Thr Asn Met Gln Asp

1075 1080 1085

Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu Asp Gly Thr Glu Arg Glu

1090 1095 1100

Val Leu Phe Thr Thr Gly Leu Ile Arg Pro Val Ala Leu Val Val Asp

1105 1110 1115 1120

Asn Thr Leu Gly Lys Leu Phe Trp Val Asp Ala Asp Leu Lys Arg Ile

1125 1130 1135

Glu Ser Cys Asp Leu Ser Gly Ala Asn Arg Leu Thr Leu Glu Asp Ala

1140 1145 1150

Asn Ile Val Gln Pro Leu Gly Leu Thr Ile Leu Gly Lys His Leu Tyr

1155 1160 1165

Trp Ile Asp Arg Gln Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr

1170 1175 1180

Gly Asp Lys Arg Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly

1185 1190 1195 1200

Ile His Ala Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro

1205 1210 1215

Cys Ala Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly
1220 1225 1230

Asp Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln
1235 1240 1245

Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln Phe
1250 1255 1260

Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp Arg Cys
1265 1270 1275 1280

Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu Gly Cys Pro
1285 1290 1295

Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly Gln Cys Val Asp
1300 1305 1310

Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln Asp Arg Ser Asp
1315 1320 1325

Glu Val Asp Cys Asp Ala Ile Cys Leu Pro Asn Gln Phe Arg Cys Ala
1330 1335 1340

Ser Gly Gln Cys Val Leu Ile Lys Gln Gln Cys Asp Ser Phe Pro Asp
1345 1350 1355 1360

Cys Ile Asp Gly Ser Asp Glu Leu Met Cys Glu Ile Thr Lys Pro Pro
1365 1370 1375

Ser Asp Asp Ser Pro Ala His Ser Ser Ala Ile Gly Pro Val Ile Gly
1380 1385 1390

Ile Ile Leu Ser Leu Phe Val Met Gly Gly Val Tyr Phe Val Cys Gln
1395 1400 1405

Arg Val Val Cys Gln Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His
1410 1415 1420

Glu Tyr Val Ser Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro

1425 1430 1435 1440

Gly Gly Ser Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser

1445 1450 1455

Met Met Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu

1460 1465 1470

Tyr Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser

1475 1480 1485

Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro

1490 1495 1500

Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser Ser Asn

1505 1510 1515 1520

Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Ile Ile Arg Gly Met

1525 1530 1535

Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp Ser Asp Tyr

1540 1545 1550

Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp Leu Asn Ser

1555 1560 1565

Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His Ser Gln Tyr Leu

1570 1575 1580

Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro Ala Thr Glu Arg Ser Tyr

1585 1590 1595 1600

Phe His Leu Phe Pro Pro Pro Pro Ser Pro Cys Thr Asp Ser Ser

1605 1610 1615

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<212> PRT

<213> Homo sapiens

<400> 4

Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu

1 5 10 15

Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser

20 25 30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala

35 40 45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp

50 55 60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr

65 70 75 80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly

85 90 95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly

100 105 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu

115 120 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val

130 135 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Lys Ala Ile Ala Leu Asp Pro

145 150 155 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Val Glu Thr Pro Arg Ile

165 170 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser

180 185 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys

195 200 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu

210 215 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro

225 230 235 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln

245 250 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys

260 265 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser

275 280 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly

290 295 300

Gly Trp Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr

305 310 315 320

Cys Ala Cys Pro Thr Gly Val Gln Met Gln Asp Asn Gly Arg Thr Cys

325 330 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu

340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln

355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu

370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala

385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn

405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp

420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr

435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile

450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu

465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val

485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu

500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu

515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys

530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp

545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala

565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys

580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg

595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg

610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys

625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His

645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr

660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His

675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Asn Ile Ser Arg Ala Phe Met

690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro

705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp

725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg

740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu

755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro

770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val

785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln

805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn

820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro

835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn

850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr

865 870 875 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His

885 890 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln

900 905 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys

915 920 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro

930 935 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile

945 950 955 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu

965 970 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr

980 985 990

Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr

995 1000 1005

Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp Arg

1010 1015 1020

Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe Trp

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Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Ser Gly Glu

1045 1050 1055

Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro Arg Ala Ile

1060 1065 1070

Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe Thr Asn Met Gln Asp

1075 1080 1085

Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu Asp Gly Thr Glu Arg Glu

1090 1095 1100

Val Leu Phe Thr Thr Gly Leu Ile Arg Pro Val Ala Leu Val Val Asp

1105 1110 1115 1120

Asn Thr Leu Gly Lys Leu Phe Trp Val Asp Ala Asp Leu Lys Arg Ile

1125 1130 1135

Glu Ser Cys Asp Leu Ser Gly Ala Asn Arg Leu Thr Leu Glu Asp Ala

1140 1145 1150

Asn Ile Val Gln Pro Leu Gly Leu Thr Ile Leu Gly Lys His Leu Tyr

1155 1160 1165

Trp Ile Asp Arg Gln Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr

1170 1175 1180

Gly Asp Lys Arg Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly

1185 1190 1195 1200

Ile His Ala Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro

1205 1210 1215

Cys Ala Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly

1220 1225 1230

Asp Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln

1235 1240 1245

Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln Phe

1250 1255 1260

Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp Arg Cys

1265 1270 1275 1280

Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu Gly Cys Pro

1285 1290 1295

Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly Gln Cys Val Asp

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Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln Asp Arg Ser Asp

1315 1320 1325

Glu Val Asp Cys Asp Ala Ile Cys Leu Pro Asn Gln Phe Arg Cys Ala

1330 1335 1340

Ser Gly Gln Cys Val Leu Ile Lys Gln Gln Cys Asp Ser Phe Pro Asp

1345 1350 1355 1360

Cys Ile Asp Gly Ser Asp Glu Leu Met Cys Glu Ile Thr Lys Pro Pro

1365 1370 1375

Ser Asp Asp Ser Pro Ala His Ser Ser Ala Ile Gly Pro Val Ile Gly

1380 1385 1390

Ile Ile Leu Ser Leu Phe Val Met Gly Gly Val Tyr Phe Val Cys Gln

1395 1400 1405

Arg Val Val Cys Gln Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His

1410 1415 1420

Glu Tyr Val Ser Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro

1425 1430 1435 1440

Gly Gly Ser Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser

1445 1450 1455

Met Met Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu

1460 1465 1470

Tyr Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser

1475 1480 1485

Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro

1490 1495 1500

Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser Ser Asn

1505 1510 1515 1520

Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Ile Ile Arg Gly Met

1525 1530 1535

Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp Ser Asp Tyr

1540 1545 1550

Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp Leu Asn Ser

1555 1560 1565

Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His Ser Gln Tyr Leu

1570 1575 1580

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<212> DNA

<213> Artificial Sequence

<220>

<223> Artificial sequence is a primer.

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<210> 25

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<212> DNA

<213> Artificial Sequence

<220>

<223> Artificial sequence is a primer.

<400> 25
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<223> Artificial sequence is a primer.

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<220>

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<220>

<223> Artificial sequence is a primer.

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<210> 29

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<212> DNA

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<220>

<223> Artificial sequence is a primer.

<400> 29
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<223> Artificial sequence is a primer.

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<220>

<223> Artificial sequence is a primer.

<400> 31

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<211> 18

<212> DNA

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<220>

<223> Artificial sequence is a primer.

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<210> 33

<211> 20

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<220>

<223> Artificial sequence is a primer.

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<220>

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<211> 56

<212> DNA

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<220>

<223> Artificial sequence is a primer.

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<210> 36

<211> 27

<212> DNA

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<220>

<223> Artificial sequence is a primer.

<400> 36
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<210> 37

<211> 27

<212> DNA

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<220>

<223> Artificial sequence is a primer.

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<210> 38

<211> 20

<212> DNA

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<400> 38
gagaggctat atccctgggc 20

<210> 39

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<212> DNA

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<223> Artificial sequence is a primer.

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<210> 40

<211> 163

<212> DNA

<213> Homo sapiens

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<211> 419

<212> DNA

<213> Homo sapiens

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<211> 221

<212> DNA

<213> Homo sapiens

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<210> 43

<211> 221

<212> DNA

<213> Homo sapiens

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<210> 44

<211> 156

<212> DNA

<213> Homo sapiens

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<210> 45

<211> 416

<212> DNA

<213> Homo sapiens

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<211> 198

<212> DNA

<213> Homo sapiens

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gaggtgaggc tcctgtgg 198

<210> 47

<211> 244

<212> DNA

<213> Homo sapiens

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ggtc 244

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<211> 313

<212> DNA

<213> Homo sapiens

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aggtagcgtg ggc 313

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<211> 255

<212> DNA

<213> Homo sapiens

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<210> 50

<211> 210

<212> DNA

<213> Homo sapiens

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<210> 51

<211> 352

<212> DNA

<213> Homo sapiens

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<210> 52

<211> 225

<212> DNA

<213> Homo sapiens

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<210> 53

<211> 235

<212> DNA

<213> Homo sapiens

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<211> 218

<212> DNA

<213> Homo sapiens

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<210> 55

<211> 234

<212> DNA

<213> Homo sapiens

<400> 55
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<210> 56

<211> 157

<212> DNA

<213> Homo sapiens

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<210> 57

<211> 272

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<211> 274

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<213> Homo sapiens

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<211> 164

<212> DNA

<213> Homo sapiens

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<211> 130

<212> DNA

<213> Homo sapiens

<400> 61

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<213> Homo sapiens

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<400> 64

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<212> PRT
<213> Homo sapiens

<400> 87

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35 40 45

Gly Thr Gln Ile Glu Asn Ile Glu Glu Asp Phe Arg Asp Gly Leu Lys
50 55 60

Leu Met Leu Leu Leu Glu Val Ile Ser Gly Glu Arg Leu Ala Lys Pro
65 70 75 80

Glu Arg Gly Lys Met Arg Val His Lys Ile Ser Asn Val Asn Lys Ala
85 90 95

Leu Asp Phe Ile Ala Ser Lys Gly Val Lys Leu Val Ser Ile Gly Ala
100 105 110

Glu Glu Ile Val Asp Gly Asn Val Lys Met Thr Leu Gly Met Ile Trp
115 120 125

Thr Ile Ile Leu Arg Phe Ala Ile Gln Asp Ile Ser Val Glu Glu Thr
130 135 140

Ser Ala Lys Glu Gly Leu Leu Leu Trp Cys Gln Arg Lys Thr Ala Pro
145 150 155 160

Tyr Lys Asn Val Asn Ile Gln Asn Phe His Ile Ser Trp Lys Asp Gly
165 170 175

Leu Gly Phe Cys Ala Leu Ile His Arg His Arg Pro Glu Leu Ile Asp
180 185 190

Tyr Gly Lys Leu Arg Lys Asp Asp Pro Leu Thr Asn Leu Asn Thr Ala
195 200 205

Phe Asp Val Ala Glu Lys Tyr Leu Asp Ile Pro Lys Met Leu Asp Ala
210 215 220

Glu Asp Ile Val Gly Thr Ala Arg Pro Asp Glu Lys Ala Ile Met Thr
225 230 235 240

Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly Ala Gln Lys Ala Glu
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Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala Val Asn Gln Glu Asn
260 265 270

Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala Ser Asp Leu Leu Glu
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Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn Arg Val Pro Glu Asn
290 295 300

Thr Met His Ala Met Gln Gln Lys Leu Glu Asp Phe Arg Asp Tyr Arg
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Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys Cys Gln Leu Glu Ile
325 330 335

Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu Ser Asn Arg Pro Ala
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Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp Ile Asn Asn Ala Trp
355 360 365

Gly Cys Leu Glu Gln Val Glu Lys Gly Tyr Glu Glu Trp Leu Leu Asn
370 375 380

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Leu Leu Lys Lys His Glu Ala Phe Glu Ser Asp Leu Ala Ala His Gln
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Asp Tyr Tyr Asp Ser Pro Ser Val Asn Ala Arg Cys Gln Lys Ile Cys
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Asp Gln Trp Asp Asn Leu Gly Ala Leu Thr Gln Lys Arg Arg Glu Ala
485 490 495
Leu Glu Arg Thr Glu Lys Leu Leu Glu Thr Ile Asp Gln Leu Tyr Leu
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Glu Tyr Ala Lys Arg Ala Ala Pro Phe Asn Asn Trp Met Glu Gly Ala
515 520 525
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Gln Gly Leu Thr Thr Ala His Glu Gln Phe Lys Ala Thr Leu Pro Asp
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Ala Asp Lys Glu Arg Leu Ala Ile Leu Gly Ile His Asn Glu Val Ser
565 570 575
Lys Ile Val Gln Thr Tyr His Val Asn Met Ala Gly Thr Asn Pro Tyr
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Thr Thr Ile Thr Pro Gln Glu Ile Asn Gly Lys Trp Asp His Val Arg
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625 630 635 640
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Ser Ile Glu Met His Gly Thr Leu Glu Asp Gln Leu Ser His Leu Arg
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Gln Tyr Glu Lys Ser Ile Val Asn Tyr Lys Pro Lys Ile Asp Gln Leu
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Glu Gly Asp His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys
690 695 700
His Thr Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu
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Leu Thr Thr Ile Ala Arg Thr Ile Asn Glu Val Glu Asn Gln Ile Leu
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740 745 750
Ala Ser Phe Asn His Phe Asp Arg Asp His Ser Gly Thr Leu Gly Pro
755 760 765
Glu Glu Phe Lys Ala Cys Leu Ile Ser Leu Gly Tyr Asp Ile Gly Asn
770 775 780
Asp Pro Gln Gly Glu Ala Glu Phe Ala Arg Ile Met Ser Ile Val Asp
785 790 795 800
Pro Asn Arg Leu Gly Val Val Thr Phe Gln Ala Phe Ile Asp Phe Met
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Ser Arg Glu Thr Ala Asp Thr Asp Thr Ala Asp Gln Val Met Ala Ser
820 825 830
Phe Lys Ile Leu Ala Gly Asp Lys Asn Tyr Ile Thr Met Asp Glu Leu

835 840 845
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35 40 45
Lys Leu Ala Ser Glu Lys Ser Glu Met Gln Arg His Tyr Val Met Tyr
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Tyr Glu Met Ser Tyr Gly Leu Asn Ile Glu Met His Lys Gln Ala Glu
65 70 75 80
Ile Val Lys Arg Leu Asn Gly Ile Cys Ala Gln Val Leu Pro Tyr Leu
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Ser Gln Glu His Gln Gln Gln Val Leu Gly Ala Ile Glu Arg Ala Lys
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Gln Val Thr Ala Pro Glu Leu Asn Ser Ile Ile Arg Gln Gln Leu Gln
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Ala His Gln Leu Ser Gln Leu Gln Ala Leu Ala Leu Pro Leu Thr Pro
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Thr Gly Leu Leu Ser Leu Ser Ala Leu Gly Ser Gln Ala His Leu Ser
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Gly Glu Lys Ser Asp
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Asp Asn Gly Pro Gln Ile Ala Tyr Val Arg Asp Phe Lys Ala Lys Val
355 360 365
Gln Tyr Phe Arg Phe Trp Cys Gln Gln Leu Ala Met Pro Gln His Ile
370 375 380
Lys Ile Thr Val Thr Arg Lys Thr Leu Phe Glu Asp Ser Phe Gln Gln
385 390 395 400
Ile Met Ser Phe Ser Pro Gln Asp Leu Arg Arg Arg Leu Trp Val Ile
405 410 415
Phe Pro Gly Glu Glu Gly Leu Asp Tyr Gly Gly Val Ala Arg Glu Trp
420 425 430
Phe Phe Leu Leu Ser His Glu Val Leu Asn Pro Met Tyr Cys Leu Phe
435 440 445
Glu Tyr Ala Gly Lys Asp Asn Tyr Cys Leu Gln Ile Asn Pro Ala Ser
450 455 460
Tyr Ile Asn Pro Asp His Leu Lys Tyr Phe Arg Phe Ile Gly Arg Phe

```
465                 470                 475                 480
Ile Ala Met Ala Leu Phe His Gly Lys Phe Ile Asp Thr Gly Phe Ser
                485                 490                 495
Leu Pro Phe Tyr Lys Arg Ile Leu Asn Lys Pro Val Gly Leu Lys Asp
            500                 505                 510
Leu Glu Ser Ile Asp Pro Glu Phe Tyr Asn Ser Leu Ile Trp Val Lys
        515                 520                 525
Glu Asn Asn Ile Glu Glu Cys Asp Leu Glu Met Tyr Phe Ser Val Asp
    530                 535                 540
Lys Glu Ile Leu Gly Glu Ile Lys Ser His Asp Leu Lys Pro Asn Gly
545                 550                 555                 560
Gly Asn Ile Leu Val Thr Glu Glu Asn Lys Glu Glu Tyr Ile Arg Met
                565                 570                 575
Val Ala Glu Trp Arg Leu Ser Arg Gly Val Glu Glu Gln Thr Gln Ala
            580                 585                 590
Phe Phe Glu Gly Phe Asn Glu Ile Leu Pro Gln Gln Tyr Leu Gln Tyr
        595                 600                 605
Phe Asp Ala Lys Glu Leu Glu Val Leu Leu Cys Gly Met Gln Glu Ile
    610                 615                 620
Asp Leu Asn Asp Trp Gln Arg His Ala Ile Tyr Arg His Tyr Ala Arg
625                 630                 635                 640
Thr Ser Lys Gln Ile Met Trp Phe Trp Gln Phe Val Lys Glu Ile Asp
                645                 650                 655
Asn Glu Lys Arg Met Arg Leu Leu Gln Phe Val Thr Gly Thr Cys Arg
            660                 665                 670
Leu Pro Val Gly Gly Phe Ala Asp Leu Met Gly Ser Asn Gly Pro Gln
        675                 680                 685
Lys Phe Cys Ile Glu Lys Val Gly Lys Glu Asn Trp Leu Pro Arg Ser
    690                 695                 700
His Thr Cys Phe Asn Arg Leu Asp Leu Pro Pro Tyr Lys Ser Tyr Glu
705                 710                 715                 720
Gln Leu Lys Glu Lys Leu Leu Phe Ala Ile Glu Glu Thr Glu Gly Phe
                725                 730                 735
Gly Gln Glu
```

<210> 90
<211> 431
<212> PRT
<213> Homo sapiens

<400> 90

```
Gly Pro Pro Pro Thr Arg Ala Leu Pro Leu Pro Gln Ser Leu Pro Pro
 1               5                  10                  15
Asp Phe Arg Leu Glu Pro Thr Ala Pro Ala Leu Ser Pro Arg Ser Ser
            20                  25                  30
Phe Ala Ser Ser Ser Ala Ser Asp Ala Ser Lys Pro Ser Ser Pro Arg
        35                  40                  45
Gly Ser Leu Leu Leu Asp Gly Ala Gly Ala Gly Gly Ala Gly Gly Ser
    50                  55                  60
Arg Pro Cys Ser Asn Arg Thr Ser Gly Ile Ser Met Gly Tyr Asp Gln
65                  70                  75                  80
Arg His Gly Ser Pro Leu Pro Ala Gly Pro Cys Leu Phe Gly Pro Pro
```

```
                    85                  90                  95
Leu Ala Gly Ala Pro Ala Gly Tyr Ser Pro Gly Gly Val Pro Ser Ala
                100                 105                 110
Tyr Pro Glu Leu His Ala Ala Leu Asp Arg Leu Tyr Ala Gln Arg Pro
        115                 120                 125
Ala Gly Phe Gly Cys Gln Glu Ser Arg His Ser Tyr Pro Pro Ala Leu
    130                 135                 140
Gly Ser Pro Gly Ala Leu Ala Gly Ala Arg Val Gly Ala Ala Gly Pro
145                 150                 155                 160
Leu Glu Arg Arg Gly Ala Gln Pro Gly Arg His Ser Val Thr Gly Tyr
                165                 170                 175
Gly Asp Cys Ala Val Gly Ala Arg Tyr Gln Asp Glu Leu Thr Ala Leu
            180                 185                 190
Leu Arg Leu Thr Val Gly Thr Gly Gly Arg Glu Ala Gly Ala Arg Gly
        195                 200                 205
Glu Pro Ser Gly Ile Glu Pro Ser Gly Leu Glu Glu Pro Pro Gly Pro
    210                 215                 220
Phe Val Pro Glu Ala Ala Arg Ala Arg Met Arg Glu Pro Glu Ala Arg
225                 230                 235                 240
Glu Asp Tyr Phe Gly Thr Cys Ile Lys Cys Asn Lys Gly Ile Tyr Gly
                245                 250                 255
Gln Ser Asn Ala Cys Gln Ala Leu Asp Ser Leu Tyr His Thr Gln Cys
            260                 265                 270
Phe Val Cys Cys Ser Cys Gly Arg Thr Leu Arg Cys Lys Ala Phe Tyr
        275                 280                 285
Ser Val Asn Gly Ser Val Tyr Cys Glu Glu Asp Tyr Leu Phe Ser Gly
    290                 295                 300
Phe Gln Glu Ala Ala Glu Lys Cys Cys Val Cys Gly His Leu Ile Leu
305                 310                 315                 320
Glu Lys Ile Leu Gln Ala Met Gly Lys Ser Tyr His Pro Gly Cys Phe
                325                 330                 335
Arg Cys Ile Val Cys Asn Lys Cys Leu Asp Gly Ile Pro Phe Thr Val
            340                 345                 350
Asp Phe Ser Asn Gln Val Tyr Cys Val Thr Asp Tyr His Lys Asn Tyr
        355                 360                 365
Ala Pro Lys Cys Ala Ala Cys Gly Gln Pro Ile Leu Pro Ser Glu Gly
    370                 375                 380
Cys Glu Asp Ile Val Arg Val Ile Ser Met Asp Arg Asp Tyr His Phe
385                 390                 395                 400
Glu Cys Tyr His Cys Glu Asp Cys Arg Met Gln Leu Ser Asp Glu Glu
                405                 410                 415
Gly Cys Cys Cys Phe Pro Leu Asp Gly His Leu Leu Cys His Gly
            420                 425                 430
```

<210> 91
<211> 900
<212> PRT
<213> Homo sapiens

<400> 91

```
Gly Pro Gly Ser Arg His His Arg Ala Arg Asp Arg Leu Ile His Phe
 1               5                  10                  15
Gly Ala Val Ser Thr Asp Val Leu Gly Cys Ser Ala His Cys Ser Leu
```

20 25 30
Thr Gln Ser Pro Lys Met Asn Ile Gln Glu Gln Gly Phe Pro Leu Asp
35 40 45
Leu Gly Ala Ser Phe Thr Glu Asp Ala Pro Arg Pro Pro Val Pro Gly
50 55 60
Glu Glu Gly Glu Leu Val Ser Thr Asp Pro Arg Pro Ala Ser Tyr Ser
65 70 75 80
Phe Cys Ser Gly Lys Gly Val Gly Ile Lys Gly Glu Thr Ser Thr Ala
85 90 95
Thr Pro Arg Arg Ser Asp Leu Asp Leu Gly Tyr Glu Pro Glu Gly Ser
100 105 110
Ala Ser Pro Thr Pro Pro Tyr Leu Lys Trp Ala Glu Ser Leu His Ser
115 120 125
Leu Leu Asp Asp Gln Asp Gly Ile Ser Leu Phe Arg Thr Phe Leu Lys
130 135 140
Gln Glu Gly Cys Ala Asp Leu Leu Asp Phe Trp Phe Ala Cys Thr Gly
145 150 155 160
Phe Arg Lys Leu Glu Pro Cys Asp Ser Asn Glu Glu Lys Arg Leu Lys
165 170 175
Leu Ala Arg Ala Ile Tyr Arg Lys Tyr Ile Leu Asp Asn Asn Gly Ile
180 185 190
Val Ser Arg Gln Thr Lys Pro Ala Thr Lys Ser Phe Ile Lys Gly Cys
195 200 205
Ile Met Lys Gln Leu Ile Asp Pro Ala Met Phe Asp Gln Ala Gln Thr
210 215 220
Glu Ile Gln Ala Thr Met Glu Glu Asn Thr Tyr Pro Ser Phe Leu Lys
225 230 235 240
Ser Asp Ile Tyr Leu Glu Tyr Thr Arg Thr Gly Ser Glu Ser Pro Lys
245 250 255
Val Cys Ser Asp Gln Ser Ser Gly Ser Gly Thr Gly Lys Gly Ile Ser
260 265 270
Gly Tyr Leu Pro Thr Leu Asn Glu Asp Glu Glu Trp Lys Cys Asp Gln
275 280 285
Asp Met Asp Glu Asp Asp Gly Arg Asp Ala Ala Pro Pro Gly Arg Leu
290 295 300
Pro Gln Lys Leu Leu Leu Glu Thr Ala Ala Pro Arg Val Ser Ser Ser
305 310 315 320
Arg Arg Tyr Ser Glu Gly Arg Glu Phe Arg Tyr Gly Ser Trp Arg Glu
325 330 335
Pro Val Asn Pro Tyr Tyr Val Asn Ala Gly Tyr Ala Leu Ala Pro Ala
340 345 350
Thr Ser Ala Asn Asp Ser Glu Gln Gln Ser Leu Ser Ser Asp Ala Asp
355 360 365
Thr Leu Ser Leu Thr Asp Ser Ser Val Asp Gly Ile Pro Pro Tyr Arg
370 375 380
Ile Arg Lys Gln His Arg Arg Glu Met Gln Glu Ser Ala Gln Val Asn
385 390 395 400
Gly Arg Val Pro Leu Pro His Ile Pro Arg Thr Tyr Arg Val Pro Lys
405 410 415
Glu Val Arg Val Glu Pro Gln Lys Phe Ala Glu Glu Leu Ile His Arg
420 425 430
Leu Glu Ala Val Gln Arg Thr Arg Glu Ala Glu Glu Lys Leu Glu Glu
435 440 445

Arg Leu Lys Arg Val Arg Met Glu Glu Glu Gly Glu Asp Gly Asp Pro
450 455 460
Ser Ser Gly Pro Pro Gly Pro Cys His Lys Leu Pro Pro Ala Pro Ala
465 470 475 480
Trp His His Phe Pro Pro Arg Leu Cys Trp Thr Trp Ala Cys Ala Gly
485 490 495
Leu Arg Asp Ala His Glu Glu Asn Pro Glu Ser Ile Leu Asp Glu His
500 505 510
Val Gln Arg Val Leu Arg Thr Thr Gly Arg Gln Ser Pro Gly Pro Gly
515 520 525
His Arg Ser Pro Asp Ser Gly His Val Ala Lys Met Pro Val Ala Leu
530 535 540
Gly Gly Ala Ala Ser Gly His Gly Lys His Val Pro Lys Ser Gly Ala
545 550 555 560
Lys Leu Asp Ala Ala Gly Leu His His His Arg His Val His His His
565 570 575
Val His His Ser Thr Ala Arg Pro Lys Glu Gln Val Glu Ala Glu Ala
580 585 590
Thr Arg Arg Ala Gln Ser Ser Phe Ala Trp Gly Leu Glu Pro His Ser
595 600 605
His Gly Ala Arg Ser Arg Gly Tyr Ser Glu Ser Val Gly Ala Ala Pro
610 615 620
Asn Ala Ser Asp Gly Leu Ala His Ser Gly Lys Val Gly Val Ala Cys
625 630 635 640
Lys Arg Asn Ala Lys Lys Ala Glu Ser Gly Lys Ser Ala Ser Thr Glu
645 650 655
Val Pro Gly Ala Ser Glu Asp Ala Glu Lys Asn Gln Lys Ile Met Gln
660 665 670
Trp Ile Ile Glu Gly Glu Lys Glu Ile Ser Arg His Arg Arg Thr Gly
675 680 685
His Gly Ser Ser Gly Thr Arg Lys Pro Gln Pro His Glu Asn Ser Arg
690 695 700
Pro Leu Ser Leu Glu His Pro Trp Ala Gly Pro Gln Leu Arg Thr Ser
705 710 715 720
Val Gln Pro Ser His Leu Phe Ile Gln Asp Pro Thr Met Pro Pro His
725 730 735
Pro Ala Pro Asn Pro Leu Thr Gln Leu Glu Glu Ala Arg Arg Arg Leu
740 745 750
Glu Glu Glu Glu Lys Arg Ala Ser Arg Ala Pro Ser Lys Gln Arg Tyr
755 760 765
Val Gln Glu Val Met Arg Arg Gly Arg Ala Cys Val Arg Pro Ala Cys
770 775 780
Ala Pro Val Leu His Val Val Pro Ala Val Ser Asp Met Glu Leu Ser
785 790 795 800
Glu Thr Glu Thr Arg Ser Gln Arg Lys Val Gly Gly Gly Ser Ala Gln
805 810 815
Pro Cys Asp Ser Ile Val Val Ala Tyr Tyr Phe Cys Gly Glu Pro Ile
820 825 830
Pro Tyr Arg Thr Leu Val Arg Gly Arg Ala Val Thr Leu Gly Gln Phe
835 840 845
Lys Glu Leu Leu Thr Lys Lys Gly Ser Tyr Arg Tyr Tyr Phe Lys Lys
850 855 860
Val Ser Asp Glu Phe Asp Cys Gly Val Val Phe Glu Glu Val Arg Glu

865 870 875 880
Asp Glu Ala Val Leu Pro Val Phe Glu Glu Lys Ile Ile Gly Lys Val
885 890 895
Glu Lys Val Asp
900

<210> 92
<211> 591
<212> PRT
<213> Homo sapiens

<400> 92
Met Val Pro Val Ala Val Thr Ala Ala Val Ala Pro Val Leu Ser Ile
1 5 10 15
Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile Lys Lys Gln Leu Leu Leu
20 25 30
Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu Leu His Ser Ser Lys Trp
35 40 45
Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala Leu Pro Leu Ala Glu Leu
50 55 60
Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp Ala Gln Asp Met Asp Ala
65 70 75 80
Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val Lys Glu Tyr Asp Arg Ala
85 90 95
Ala His Phe Leu His Gly Cys Asn Ser Lys Lys Ala Tyr Phe Leu Tyr
100 105 110
Met Tyr Ser Arg Tyr Leu Ser Gly Glu Lys Lys Lys Asp Asp Glu Thr
115 120 125
Val Asp Ser Leu Gly Pro Leu Glu Lys Gly Gln Val Lys Asn Glu Ala
130 135 140
Leu Arg Glu Leu Arg Val Glu Leu Ser Lys Lys His Gln Ala Arg Glu
145 150 155 160
Leu Asp Gly Phe Gly Leu Tyr Leu Tyr Gly Val Val Leu Arg Lys Leu
165 170 175
Asp Leu Val Lys Glu Ala Ile Asp Val Phe Val Glu Ala Thr His Val
180 185 190
Leu Pro Leu His Trp Gly Ala Trp Leu Glu Leu Cys Asn Leu Ile Thr
195 200 205
Asp Lys Glu Met Leu Lys Phe Leu Ser Leu Pro Asp Thr Trp Met Lys
210 215 220
Glu Phe Phe Leu Ala His Ile Tyr Thr Glu Leu Gln Leu Ile Glu Glu
225 230 235 240
Ala Leu Gln Lys Tyr Gln Asn Leu Ile Asp Val Gly Phe Ser Lys Ser
245 250 255
Ser Tyr Ile Val Ser Gln Ile Ala Val Ala Tyr His Asn Ile Arg Asp
260 265 270
Ile Asp Lys Ala Leu Ser Ile Phe Asn Glu Leu Arg Lys Gln Asp Pro
275 280 285
Tyr Arg Ile Glu Asn Met Asp Thr Phe Ser Asn Leu Leu Tyr Val Arg
290 295 300
Ser Met Lys Ser Glu Leu Ser Tyr Leu Ala His Asn Leu Cys Glu Ile
305 310 315 320
Asp Lys Tyr Arg Val Glu Thr Cys Cys Val Ile Gly Asn Tyr Tyr Ser

```
                325                 330                 335
Leu Arg Ser Gln His Glu Lys Ala Ala Leu Tyr Phe Gln Arg Ala Leu
            340                 345                 350
Lys Leu Asn Pro Arg Tyr Leu Gly Ala Trp Thr Leu Met Gly His Glu
        355                 360                 365
Tyr Met Glu Met Lys Asn Thr Ser Ala Ala Ile Gln Ala Tyr Arg His
    370                 375                 380
Ala Ile Glu Val Asn Lys Arg Asp Tyr Arg Ala Trp Tyr Gly Leu Gly
385                 390                 395                 400
Gln Thr Tyr Glu Ile Leu Lys Met Pro Phe Tyr Cys Leu Tyr Tyr Tyr
                405                 410                 415
Arg Arg Ala His Gln Leu Arg Pro Asn Asp Ser Arg Met Leu Val Ala
            420                 425                 430
Leu Gly Glu Cys Tyr Glu Lys Leu Asn Gln Leu Val Glu Ala Lys Lys
        435                 440                 445
Cys Tyr Trp Arg Ala Tyr Ala Val Gly Asp Val Glu Lys Met Ala Leu
    450                 455                 460
Val Lys Leu Ala Lys Leu His Glu Gln Leu Thr Glu Ser Glu Gln Ala
465                 470                 475                 480
Ala Gln Cys Tyr Ile Lys Tyr Ile Gln Asp Ile Tyr Ser Cys Gly Glu
                485                 490                 495
Ile Val Glu His Leu Glu Glu Ser Thr Ala Phe Arg Tyr Leu Ala Gln
            500                 505                 510
Tyr Tyr Phe Lys Cys Lys Leu Trp Asp Glu Ala Ser Thr Cys Ala Gln
        515                 520                 525
Lys Cys Cys Ala Phe Asn Asp Thr Arg Glu Glu Gly Lys Ala Leu Leu
    530                 535                 540
Arg Gln Ile Leu Gln Leu Arg Asn Gln Gly Glu Thr Pro Thr Thr Glu
545                 550                 555                 560
Val Pro Ala Pro Phe Phe Leu Pro Ala Ser Leu Ser Ala Asn Asn Thr
                565                 570                 575
Pro Thr Arg Arg Val Ser Pro Leu Asn Leu Ser Ser Val Thr Pro
            580                 585                 590

<210> 93
<211> 914
<212> PRT
<213> Homo sapiens

<400> 93
Val Tyr Gln Val Leu Leu Val Gly Ser Thr Leu Leu Lys Glu Val Pro
1               5                   10                  15
Ser Gly Leu Gln Leu Glu Gln Leu Pro Ser Gln Ser Leu Leu Thr His
            20                  25                  30
Ile Pro Thr Ala Gly Leu Pro Thr Ser Leu Gly Gly Gly Leu Pro Tyr
        35                  40                  45
Cys His Gln Ala Trp Leu Asp Phe Arg Arg Arg Leu Glu Ala Leu Leu
    50                  55                  60
Gln Asn Cys Gln Ala Ala Cys Ala Leu Leu Gln Gly Ala Ile Glu Ser
65                  70                  75                  80
Val Lys Ala Val Pro Gln Pro Met Glu Pro Gly Glu Val Gly Gln Leu
                85                  90                  95
Leu Gln Gln Thr Glu Val Leu Met Gln Gln Val Leu Asp Ser Pro Trp
```

```
                100                 105                 110
Leu Ala Trp Leu Gln Cys Gln Gly Gly Arg Glu Leu Thr Trp Leu Lys
            115                 120                 125
Gln Glu Val Pro Glu Val Thr Leu Ser Pro Asp Tyr Arg Thr Ala Met
    130                 135                 140
Asp Lys Ala Asp Glu Leu Tyr Asp Arg Val Asp Gly Leu Leu His Gln
145                 150                 155                 160
Leu Thr Leu Gln Ser Asn Gln Arg Ile Gln Ala Leu Glu Leu Val Gln
                165                 170                 175
Thr Leu Glu Ala Arg Glu Ser Gly Leu His Gln Ile Glu Val Trp Leu
            180                 185                 190
Gln Gln Val Gly Trp Pro Ala Leu Glu Glu Ala Gly Glu Pro Ser Leu
        195                 200                 205
Asp Met Leu Leu Gln Ala Gln Gly Ser Phe Gln Glu Leu Tyr Gln Val
    210                 215                 220
Ala Gln Glu Gln Val Arg Gln Gly Glu Lys Phe Leu Gln Pro Leu Thr
225                 230                 235                 240
Gly Trp Glu Ala Ala Glu Leu Asp Pro Pro Gly Ala Arg Phe Leu Ala
                245                 250                 255
Leu Arg Ala Gln Leu Thr Glu Phe Ser Arg Ala Leu Ala Gln Arg Cys
            260                 265                 270
Gln Arg Leu Ala Asp Ala Glu Arg Leu Phe Gln Leu Phe Arg Glu Ala
        275                 280                 285
Leu Thr Trp Ala Glu Glu Gly Gln Arg Val Leu Ala Glu Leu Glu Gln
    290                 295                 300
Glu Arg Pro Gly Val Val Leu Gln Gln Leu Gln Leu His Trp Thr Arg
305                 310                 315                 320
His Pro Asp Leu Pro Pro Ala His Phe Arg Lys Met Trp Ala Leu Ala
                325                 330                 335
Thr Gly Leu Gly Ser Glu Ala Ile Arg Gln Glu Cys Arg Trp Ala Trp
            340                 345                 350
Ala Arg Cys Gln Asp Thr Trp Leu Ala Leu Asp Gln Lys Leu Glu Ala
        355                 360                 365
Ser Leu Lys Leu Pro Pro Val Gly Ser Thr Ala Ser Leu Cys Val Ser
    370                 375                 380
Gln Val Pro Ala Ala Pro Ala His Pro Pro Leu Arg Lys Ala Tyr Ser
385                 390                 395                 400
Phe Asp Arg Asn Leu Gly Gln Ser Leu Ser Glu Pro Ala Cys His Cys
                405                 410                 415
His His Ala Ala Thr Ile Ala Ala Cys Arg Arg Pro Glu Ala Gly Gly
            420                 425                 430
Gly Ala Leu Pro Gln Ala Ser Pro Thr Val Pro Pro Pro Gly Ser Ser
        435                 440                 445
Asp Pro Arg Ser Leu Asn Arg Leu Gln Leu Val Leu Ala Glu Met Val
    450                 455                 460
Ala Thr Glu Arg Glu Tyr Val Arg Ala Leu Glu Tyr Thr Met Glu Asn
465                 470                 475                 480
Tyr Phe Pro Glu Leu Asp Arg Pro Asp Val Pro Gln Gly Leu Arg Gly
                485                 490                 495
Gln Arg Ala His Leu Phe Gly Asn Leu Glu Lys Leu Arg Asp Phe His
            500                 505                 510
Cys His Phe Phe Leu Arg Glu Leu Glu Ala Cys Thr Arg His Pro Pro
        515                 520                 525
```

Arg Val Ala Tyr Ala Phe Leu Arg His Arg Val Gln Phe Gly Met Tyr
530 535 540

Ala Leu Tyr Ser Lys Asn Lys Pro Arg Ser Asp Ala Leu Met Ser Ser
545 550 555 560

Tyr Gly His Thr Phe Phe Lys Asp Lys Gln Gln Ala Leu Gly Asp His
565 570 575

Leu Asp Leu Ala Ser Tyr Leu Leu Lys Pro Ile Gln Arg Met Gly Lys
580 585 590

Tyr Ala Leu Leu Leu Gln Glu Leu Ala Arg Ala Cys Gly Gly Pro Thr
595 600 605

Gln Glu Leu Ser Ala Leu Arg Glu Ala Gln Ser Leu Val His Phe Gln
610 615 620

Leu Arg His Gly Asn Asp Leu Leu Ala Met Asp Ala Ile Gln Gly Cys
625 630 635 640

Asp Val Asn Leu Lys Glu Gln Gly Gln Leu Val Arg Gln Asp Glu Phe
645 650 655

Val Val Arg Thr Gly Arg His Lys Ser Val Arg Arg Ile Phe Leu Phe
660 665 670

Glu Glu Leu Leu Leu Phe Ser Lys Pro Arg His Gly Pro Thr Gly Val
675 680 685

Asp Thr Phe Ala Tyr Lys Arg Ser Phe Lys Met Ala Asp Leu Gly Leu
690 695 700

Thr Glu Cys Cys Gly Asn Ser Asn Leu Arg Phe Glu Ile Trp Phe Arg
705 710 715 720

Arg Arg Lys Ala Arg Asp Thr Phe Val Leu Gln Ala Ser Ser Leu Ala
725 730 735

Ile Lys Gln Ala Trp Thr Ala Asp Ile Ser His Leu Leu Trp Arg Gln
740 745 750

Ala Val His Asn Lys Glu Val Arg Met Ala Glu Met Val Ser Met Gly
755 760 765

Val Gly Asn Lys Ala Phe Arg Asp Ile Ala Pro Ser Glu Glu Ala Ile
770 775 780

Asn Asp Arg Thr Val Asn Tyr Val Leu Lys Cys Arg Glu Val Arg Ser
785 790 795 800

Arg Ala Ser Ile Ala Val Ala Pro Phe Asp His Asp Ser Leu Tyr Leu
805 810 815

Gly Ala Ser Asn Ser Leu Pro Gly Asp Pro Ala Ser Cys Ser Val Leu
820 825 830

Gly Ser Leu Asn Leu His Leu Tyr Arg Asp Pro Ala Leu Leu Gly Leu
835 840 845

Arg Cys Pro Leu Tyr Pro Ser Phe Leu Glu Glu Ala Ala Leu Glu Ala
850 855 860

Glu Ala Glu Leu Gly Gly Gln Pro Ser Leu Thr Ala Glu Asp Ser Glu
865 870 875 880

Ile Ser Ser Gln Cys Pro Ser Ala Ser Gly Ser Ser Gly Ser Asp Ser
885 890 895

Ser Cys Val Ser Gly Gln Ala Leu Gly Arg Gly Leu Glu Asp Leu Pro
900 905 910

Cys Val

<210> 94
<211> 277

<212> PRT
<213> Homo sapiens

<400> 94
Leu Asn Tyr Leu Leu Glu Ser Arg Leu Glu Ala Ala Ala His Cys Ala
1 5 10 15
Leu Lys Gln Gly Ile Ala Thr Ala Ser Leu Leu Pro Ala Gln Leu Gln
20 25 30
Pro Ala Val Leu Thr Val Val Thr Cys His Val Val Val Ser Val His
35 40 45
Gly His His Thr Asp Gly Cys Leu Ala Ala Leu Cys Arg Glu Asp Arg
50 55 60
Thr Gly Thr Gly Gly Ala Phe Trp Cys Lys Asn Arg Val Ile Val Ser
65 70 75 80
His Ala Val Asp Val Val Leu His Val His Gly Glu Gly Asn Pro Val
85 90 95
Gln Ala Leu Ile Ala His Gly Ala Pro Glu Ala Ala Trp Val Val Gly
100 105 110
Leu Ala Gln Gly Leu Gln Asp His Phe His Asp Glu Met Ser Thr His
115 120 125
Ala Ala Phe Val Gly Arg Leu Leu Glu Pro Gly Val Gln Glu Val Leu
130 135 140
Leu Ala Val His Phe Leu Thr His Val Val Glu Arg Leu Pro Thr Glu
145 150 155 160
Ser Ser Pro Thr Arg Val Ala Gly Glu Ala Val Ser Val Ile Lys Thr
165 170 175
Pro His Cys Leu Ala Arg Leu Leu Gly Ser Val Asp Ala Lys Pro Thr
180 185 190
Leu Asp Ala Asn Ala Glu Val Val Pro Arg Arg Ala Arg Leu Glu Arg
195 200 205
Pro Leu Gln Leu Pro Gly Glu Arg Leu Gln Pro Pro Leu Gly Arg Ala
210 215 220
Trp Ala Ala Leu Pro Ala Arg Gly Gln Arg Glu Cys Arg Gln Arg Glu
225 230 235 240
Gly Gly Arg Pro Arg Arg Leu Arg Gly Ala Ser Gly Arg Gly Ala Gly
245 250 255
Ala Gly Arg Glu Glu Val Ser Val Gly Phe Ser Ala Gln Trp Glu Phe
260 265 270
Gly Ser Gly Arg His
275

<210> 95
<211> 1120
<212> PRT
<213> Homo sapiens

<400> 95
Met Trp Arg Val Lys Lys Leu Ser Leu Ser Leu Ser Pro Ser Pro Gln
1 5 10 15
Thr Gly Lys Pro Ser Met Arg Thr Pro Leu Arg Glu Leu Thr Leu Gln
20 25 30
Pro Gly Ala Leu Thr Thr Ser Gly Lys Arg Ser Pro Ala Cys Ser Ser
35 40 45

Leu Thr Pro Ser Leu Cys Lys Leu Gly Leu Gln Glu Gly Ser Asn Asn
50 55 60
Ser Ser Pro Val Asp Phe Val Asn Asn Lys Arg Thr Asp Leu Ser Ser
65 70 75 80
Glu His Phe Ser His Ser Ser Lys Trp Leu Glu Thr Cys Gln His Glu
85 90 95
Ser Asp Glu Gln Pro Leu Asp Pro Ile Pro Gln Ile Ser Ser Thr Pro
100 105 110
Lys Thr Ser Glu Glu Ala Val Asp Pro Leu Gly Asn Tyr Met Val Lys
115 120 125
Thr Ile Val Leu Val Pro Ser Pro Leu Gly Gln Gln Gln Asp Met Ile
130 135 140
Phe Glu Ala Arg Leu Asp Thr Met Ala Glu Thr Asn Ser Ile Ser Leu
145 150 155 160
Asn Gly Pro Leu Arg Thr Asp Asp Leu Val Arg Glu Glu Val Ala Pro
165 170 175
Cys Met Gly Asp Arg Phe Ser Glu Val Ala Ala Val Ser Glu Lys Pro
180 185 190
Ile Phe Gln Glu Ser Pro Ser His Leu Leu Glu Glu Ser Pro Pro Asn
195 200 205
Pro Cys Ser Glu Gln Leu His Cys Ser Lys Glu Ser Leu Ser Ser Arg
210 215 220
Thr Glu Ala Val Arg Glu Asp Leu Val Pro Ser Glu Ser Asn Ala Phe
225 230 235 240
Leu Pro Ser Ser Val Leu Trp Leu Ser Pro Ser Thr Ala Leu Ala Ala
245 250 255
Asp Phe Arg Val Asn His Val Asp Pro Glu Glu Glu Ile Val Glu His
260 265 270
Gly Ala Met Glu Glu Arg Glu Met Arg Phe Pro Thr His Pro Lys Glu
275 280 285
Ser Glu Thr Glu Asp Gln Ala Leu Val Ser Ser Val Glu Asp Ile Leu
290 295 300
Ser Thr Cys Leu Thr Pro Asn Leu Val Glu Met Glu Ser Gln Glu Ala
305 310 315 320
Pro Gly Pro Ala Val Glu Asp Val Gly Arg Ile Leu Gly Ser Asp Thr
325 330 335
Glu Ser Trp Met Ser Pro Leu Ala Trp Leu Glu Lys Gly Val Asn Thr
340 345 350
Ser Val Met Leu Glu Asn Leu Arg Gln Ser Leu Ser Leu Pro Ser Met
355 360 365
Leu Arg Asp Ala Ala Ile Gly Thr Thr Pro Phe Ser Thr Cys Ser Val
370 375 380
Gly Thr Trp Phe Thr Pro Ser Ala Pro Gln Glu Lys Ser Thr Asn Thr
385 390 395 400
Ser Gln Thr Gly Leu Val Gly Thr Lys His Ser Thr Ser Glu Thr Glu
405 410 415
Gln Leu Leu Cys Gly Arg Pro Pro Asp Leu Thr Ala Leu Ser Arg His
420 425 430
Asp Leu Glu Asp Asn Leu Leu Ser Ser Leu Val Ile Val Glu Phe Leu
435 440 445
Ser Arg Gln Leu Arg Asp Trp Lys Ser Gln Leu Ala Val Pro His Pro
450 455 460
Glu Thr Gln Asp Ser Ser Thr Gln Thr Asp Thr Ser His Ser Gly Ile

465 470 475 480
Thr Asn Lys Leu Gln His Leu Lys Glu Ser His Glu Met Gly Gln Ala
485 490 495
Leu Gln Gln Ala Arg Asn Val Met Gln Ser Trp Val Leu Ile Ser Lys
500 505 510
Glu Leu Ile Ser Leu Leu His Leu Ser Leu Leu His Leu Glu Glu Asp
515 520 525
Lys Thr Thr Val Asn Gln Glu Ser Arg Arg Ala Glu Thr Leu Val Cys
530 535 540
Cys Cys Phe Asp Leu Leu Lys Lys Leu Arg Ala Lys Leu Gln Ser Leu
545 550 555 560
Lys Ala Glu Arg Glu Glu Ala Arg His Arg Glu Glu Met Ala Leu Arg
565 570 575
Gly Lys Asp Ala Ala Glu Ile Val Leu Glu Ala Phe Cys Ala His Ala
580 585 590
Ser Gln Arg Ile Ser Gln Leu Glu Gln Asp Leu Ala Ser Met Arg Glu
595 600 605
Phe Arg Gly Leu Leu Lys Asp Ala Gln Thr Gln Leu Val Gly Leu His
610 615 620
Ala Lys Gln Glu Glu Leu Val Gln Gln Thr Val Ser Leu Thr Ser Thr
625 630 635 640
Leu Gln Gln Asp Trp Arg Ser Met Gln Leu Asp Tyr Thr Thr Trp Thr
645 650 655
Ala Leu Leu Ser Arg Ser Arg Gln Leu Thr Glu Lys Leu Thr Val Lys
660 665 670
Ser Gln Gln Ala Leu Gln Glu Arg Asp Val Ala Ile Glu Glu Lys Gln
675 680 685
Glu Val Ser Arg Val Leu Glu Gln Val Ser Ala Gln Leu Glu Glu Cys
690 695 700
Lys Gly Gln Thr Glu Gln Leu Glu Leu Glu Asn Ile Arg Leu Ala Thr
705 710 715 720
Asp Leu Arg Ala Gln Leu Gln Ile Leu Ala Asn Met Asp Ser Gln Leu
725 730 735
Lys Glu Leu Gln Ser Gln His Thr His Cys Ala Gln Asp Leu Ala Met
740 745 750
Lys Asp Glu Leu Leu Cys Gln Leu Thr Gln Ser Asn Glu Glu Gln Ala
755 760 765
Ala Gln Cys Val Lys Glu Glu Met Ala Leu Lys His Met Gln Ala Glu
770 775 780
Leu Gln Gln Gln Gln Ala Val Leu Ala Lys Glu Val Arg Asp Leu Lys
785 790 795 800
Glu Thr Leu Glu Phe Ala Asp Gln Glu Asn Gln Val Ala His Leu Glu
805 810 815
Leu Gly Gln Val Glu Cys Gln Leu Lys Thr Thr Leu Glu Val Leu Arg
820 825 830
Glu Arg Ser Leu Gln Cys Glu Asn Leu Lys Asp Thr Val Glu Asn Leu
835 840 845
Thr Ala Lys Leu Ala Ser Thr Ile Ala Asp Asn Gln Glu Gln Asp Leu
850 855 860
Glu Lys Thr Arg Gln Tyr Ser Gln Lys Leu Gly Leu Leu Thr Glu Gln
865 870 875 880
Leu Gln Ser Leu Thr Leu Phe Leu Gln Thr Lys Leu Lys Glu Lys Thr
885 890 895

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Glu Gln Glu Thr Leu Leu Leu Ser Thr Ala Cys Pro Pro Thr Gln Glu
            900                 905                 910
His Pro Leu Pro Asn Asp Arg Thr Phe Leu Gly Ser Ile Leu Thr Ala
        915                 920                 925
Val Ala Asp Glu Glu Pro Glu Ser Thr Pro Val Pro Leu Leu Gly Ser
    930                 935                 940
Asp Lys Ser Ala Phe Thr Arg Val Ala Ser Met Val Ser Leu Gln Pro
945                 950                 955                 960
Ala Glu Thr Pro Gly Met Glu Glu Ser Leu Ala Glu Met Ser Ile Met
                965                 970                 975
Thr Thr Glu Leu Gln Ser Leu Cys Ser Leu Leu Gln Glu Ser Lys Glu
            980                 985                 990
Glu Ala Ile Arg Thr Leu Gln Arg Lys Ile Cys Glu Leu Gln Ala Arg
        995                 1000                1005
Leu Gln Ala Gln Glu Glu Gln His Gln Glu Val Gln Lys Ala Lys Glu
    1010                1015                1020
Ala Asp Ile Glu Lys Leu Asn Gln Ala Leu Cys Leu Arg Tyr Lys Asn
1025                1030                1035                1040
Glu Lys Glu Leu Gln Glu Val Ile Gln Gln Asn Glu Lys Ile Leu Glu
                1045                1050                1055
Gln Ile Asp Lys Ser Gly Glu Leu Ile Ser Leu Arg Glu Glu Val Thr
            1060                1065                1070
His Leu Thr Arg Ser Leu Arg Arg Ala Glu Thr Glu Thr Lys Val Leu
        1075                1080                1085
Gln Glu Ala Trp Gln Ala Ser Trp Thr Pro Thr Ala Ser Leu Trp Pro
    1090                1095                1100
Pro Ile Gly Ser Arg Arg Lys Cys Gly Ser Leu Arg Arg Trp Thr Asn
1105                1110                1115                1120

<210> 96
<211> 540
<212> PRT
<213> Homo sapiens

<400> 96
Met Gly Thr Thr Ala Arg Ala Ala Leu Val Leu Thr Tyr Leu Ala Val
 1               5                  10                  15
Ala Ser Ala Ala Ser Glu Gly Gly Phe Thr Ala Thr Gly Gln Arg Gln
            20                  25                  30
Leu Arg Pro Glu His Phe Gln Glu Val Gly Tyr Ala Ala Pro Pro Ser
        35                  40                  45
Pro Pro Leu Ser Arg Ser Leu Pro Met Asp His Pro Asp Ser Ser Gln
    50                  55                  60
His Gly Pro Pro Phe Glu Gly Gln Ser Gln Val Gln Pro Pro Pro Ser
65                  70                  75                  80
Gln Glu Ala Thr Pro Leu Gln Gln Glu Lys Leu Leu Pro Ala Gln Leu
                85                  90                  95
Pro Ala Glu Lys Glu Val Gly Pro Pro Leu Pro Gln Glu Ala Val Pro
            100                 105                 110
Leu Gln Lys Glu Leu Pro Ser Leu Gln His Pro Asn Glu Gln Lys Glu
        115                 120                 125
Gly Thr Pro Ala Pro Phe Gly Asp Gln Ser His Pro Glu Pro Glu Ser
    130                 135                 140
```

Trp Asn Ala Ala Gln His Cys Gln Gln Asp Arg Ser Gln Gly Gly Trp
145 150 155 160
Gly His Arg Leu Asp Gly Phe Pro Pro Gly Arg Pro Ser Pro Asp Asn
165 170 175
Leu Asn Gln Ile Cys Leu Pro Asn Arg Gln His Val Val Tyr Gly Pro
180 185 190
Trp Asn Leu Pro Gln Ser Ser Tyr Ser His Leu Thr Arg Gln Gly Glu
195 200 205
Thr Leu Asn Phe Leu Glu Ile Gly Tyr Ser Arg Cys Cys His Cys Arg
210 215 220
Ser His Thr Asn Arg Leu Glu Cys Ala Lys Leu Val Trp Glu Glu Ala
225 230 235 240
Met Ser Arg Phe Cys Glu Ala Glu Phe Ser Val Lys Thr Arg Pro His
245 250 255
Trp Cys Cys Thr Arg Gln Gly Glu Ala Arg Phe Ser Cys Phe Gln Glu
260 265 270
Glu Ala Pro Gln Pro His Tyr Gln Leu Arg Ala Cys Pro Ser His Gln
275 280 285
Pro Asp Ile Ser Ser Gly Leu Glu Leu Pro Phe Pro Pro Gly Val Pro
290 295 300
Thr Leu Asp Asn Ile Lys Asn Ile Cys His Leu Arg Arg Phe Arg Ser
305 310 315 320
Val Pro Arg Asn Leu Pro Ala Thr Asp Pro Leu Gln Arg Glu Leu Leu
325 330 335
Ala Leu Ile Gln Leu Glu Arg Glu Phe Gln Arg Cys Cys Arg Gln Gly
340 345 350
Asn Asn His Thr Cys Thr Trp Lys Ala Trp Glu Asp Thr Leu Asp Lys
355 360 365
Tyr Cys Asp Arg Glu Tyr Ala Val Lys Thr His His His Leu Cys Cys
370 375 380
Arg His Pro Pro Ser Pro Thr Arg Asp Glu Cys Phe Ala Arg Arg Ala
385 390 395 400
Pro Tyr Pro Asn Tyr Asp Arg Asp Ile Leu Thr Ile Asp Ile Ser Arg
405 410 415
Val Thr Pro Asn Leu Met Gly His Leu Cys Gly Asn Gln Arg Val Leu
420 425 430
Thr Lys His Lys His Ile Pro Gly Leu Ile His Asn Met Thr Ala Arg
435 440 445
Cys Cys Asp Leu Pro Phe Pro Glu Gln Ala Cys Cys Ala Glu Glu Glu
450 455 460
Lys Leu Thr Phe Ile Asn Asp Leu Cys Gly Pro Arg Arg Asn Ile Trp
465 470 475 480
Arg Asp Pro Ala Leu Cys Cys Tyr Leu Ser Pro Gly Asp Glu Gln Val
485 490 495
Asn Cys Phe Asn Ile Asn Tyr Leu Arg Asn Val Ala Leu Val Ser Gly
500 505 510
Asp Thr Glu Asn Ala Lys Gly Gln Gly Glu Gln Gly Ser Thr Gly Gly
515 520 525
Thr Asn Ile Ser Ser Thr Ser Glu Pro Lys Glu Glu
530 535 540

<210> 97
<211> 462

<212> PRT
<213> Homo sapiens

<400> 97
Met Gly Lys Glu Lys Thr His Ile Asn Ile Val Val Ile Gly His Val
1 5 10 15
Asp Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly
20 25 30
Gly Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu
35 40 45
Met Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys
50 55 60
Ala Glu Arg Glu Arg Gly Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe
65 70 75 80
Glu Thr Ser Lys Tyr Tyr Val Thr Ile Ile Asp Ala Pro Gly His Arg
85 90 95
Asp Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala
100 105 110
Val Leu Ile Val Ala Ala Gly Val Gly Glu Phe Glu Ala Gly Ile Ser
115 120 125
Lys Asn Gly Gln Thr Arg Glu His Ala Leu Leu Ala Tyr Thr Leu Gly
130 135 140
Val Lys Gln Leu Ile Val Gly Val Asn Lys Met Asp Ser Thr Glu Pro
145 150 155 160
Pro Tyr Ser Gln Lys Arg Tyr Glu Glu Ile Val Lys Glu Val Ser Thr
165 170 175
Tyr Ile Lys Lys Ile Gly Tyr Asn Pro Asp Thr Val Ala Phe Val Pro
180 185 190
Ile Ser Gly Trp Asn Gly Asp Asn Met Leu Glu Pro Ser Ala Asn Met
195 200 205
Pro Trp Phe Lys Gly Trp Lys Val Thr Arg Lys Asp Gly Asn Ala Ser
210 215 220
Gly Thr Thr Leu Leu Glu Ala Val Asp Cys Ile Leu Pro Pro Thr Arg
225 230 235 240
Pro Thr Asp Lys Pro Leu Arg Leu Pro Leu Gln Asp Val Tyr Lys Ile
245 250 255
Gly Gly Ile Gly Thr Val Pro Val Gly Arg Val Glu Thr Gly Val Leu
260 265 270
Lys Pro Gly Met Val Val Thr Phe Ala Pro Val Asn Val Thr Thr Glu
275 280 285
Val Lys Ser Val Glu Met His His Glu Ala Leu Ser Glu Ala Leu Pro
290 295 300
Gly Asp Asn Val Gly Phe Asn Val Lys Asn Val Ser Val Lys Asp Val
305 310 315 320
Arg Arg Gly Asn Val Ala Gly Asp Ser Lys Asn Asp Pro Pro Met Glu
325 330 335
Ala Ala Gly Phe Thr Ala Gln Val Ile Ile Leu Asn His Pro Gly Gln
340 345 350
Ile Ser Ala Gly Tyr Ala Pro Val Leu Asp Cys His Thr Ala His Ile
355 360 365
Ala Cys Lys Phe Ala Glu Leu Lys Glu Lys Ile Asp Arg Arg Ser Gly
370 375 380
Lys Lys Leu Glu Asp Gly Pro Lys Phe Leu Lys Ser Gly Asp Ala Ala

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385                 390                 395                 400
Ile Val Asp Met Val Pro Gly Lys Pro Met Cys Val Glu Ser Phe Ser
                405                 410                 415
Asp Tyr Pro Pro Leu Gly Arg Phe Ala Val Arg Asp Met Arg Gln Thr
            420                 425                 430
Val Ala Val Gly Val Ile Lys Ala Val Asp Lys Lys Ala Ala Gly Ala
        435                 440                 445
Gly Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Lys
    450                 455                 460

<210> 98
<211> 2328
<212> PRT
<213> Homo sapiens

<400> 98
Lys Ser Lys Arg Gln Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val
1               5                   10                  15
Ala Val Ser Gln Ser Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr
            20                  25                  30
Gln Ile Asn Gln Gln Trp Glu Arg Thr Tyr Leu Gly Asn Val Leu Val
        35                  40                  45
Cys Thr Cys Tyr Gly Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro
    50                  55                  60
Glu Ala Glu Glu Thr Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg
65                  70                  75                  80
Val Gly Asp Thr Tyr Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys
                85                  90                  95
Thr Cys Ile Gly Ala Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn
            100                 105                 110
Arg Cys His Glu Gly Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg
        115                 120                 125
Arg Pro His Glu Thr Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly
    130                 135                 140
Asn Gly Lys Gly Glu Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe
145                 150                 155                 160
Asp His Ala Ala Gly Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys
                165                 170                 175
Pro Tyr Gln Gly Trp Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly
            180                 185                 190
Ser Gly Arg Ile Thr Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp
        195                 200                 205
Thr Arg Thr Ser Tyr Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn
    210                 215                 220
Arg Gly Asn Leu Leu Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu
225                 230                 235                 240
Trp Lys Cys Glu Arg His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser
                245                 250                 255
Gly Pro Phe Thr Asp Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His
            260                 265                 270
Pro Gln Pro Pro Pro Tyr Gly His Cys Val Thr Asp Ser Gly Val Val
        275                 280                 285
Tyr Ser Val Gly Met Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met
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        290                 295                 300
Leu Cys Thr Cys Leu Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val
305                 310                 315                 320
Thr Gln Thr Tyr Gly Gly Asn Leu Asn Gly Glu Pro Cys Val Leu Pro
                325                 330                 335
Phe Thr Tyr Asn Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg
            340                 345                 350
Gln Asp Gly His Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp
        355                 360                 365
Gln Lys Tyr Ser Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Gln
    370                 375                 380
Gly Gly Asn Ser Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn
385                 390                 395                 400
Asn His Asn Tyr Thr Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met
                405                 410                 415
Lys Trp Cys Gly Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly
            420                 425                 430
Phe Cys Pro Met Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly
        435                 440                 445
Val Met Tyr Arg Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly
    450                 455                 460
His Met Met Arg Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr
465                 470                 475                 480
Cys Ile Ala Tyr Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile
                485                 490                 495
Thr Tyr Asn Val Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His
            500                 505                 510
Met Leu Asn Cys Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys
        515                 520                 525
Asp Pro Val Asp Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln
    530                 535                 540
Ile Gly Asp Ser Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys
545                 550                 555                 560
Tyr Cys Tyr Gly Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln
                565                 570                 575
Thr Tyr Pro Ser Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr
            580                 585                 590
Pro Ser Gln Pro Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro
        595                 600                 605
Ser His Ile Ser Lys Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val
    610                 615                 620
Gly Arg Trp Lys Glu Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr
625                 630                 635                 640
Ile Lys Gly Leu Lys Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser
                645                 650                 655
Ile Gln Gln Tyr Gly His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr
            660                 665                 670
Thr Ser Thr Ser Thr Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr
        675                 680                 685
Thr Pro Phe Ser Pro Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile
    690                 695                 700
Thr Ala Ser Ser Phe Val Val Ser Trp Val Ser Ala Ser Asp Thr Val
705                 710                 715                 720
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Ser Gly Phe Arg Val Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro
725 730 735
Gln Tyr Leu Asp Leu Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp
740 745 750
Leu Leu Pro Gly Arg Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu
755 760 765
Asp Gly Glu Gln Ser Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro
770 775 780
Asp Ala Pro Pro Asp Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile
785 790 795 800
Val Val Arg Trp Ser Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile
805 810 815
Val Tyr Ser Pro Ser Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro
820 825 830
Glu Thr Ala Asn Ser Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln
835 840 845
Tyr Asn Ile Thr Ile Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro
850 855 860
Val Val Ile Gln Gln Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val
865 870 875 880
Pro Ser Pro Arg Asp Leu Gln Phe Val Glu Val Thr Asp Val Lys Val
885 890 895
Thr Ile Met Trp Thr Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val
900 905 910
Asp Val Ile Pro Val Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro
915 920 925
Ile Ser Arg Asn Thr Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val
930 935 940
Thr Tyr Tyr Phe Lys Val Phe Ala Val Ser His Gly Arg Glu Ser Lys
945 950 955 960
Pro Leu Thr Ala Gln Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu
965 970 975
Gln Phe Val Asn Glu Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro
980 985 990
Pro Arg Ala Gln Ile Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg
995 1000 1005
Arg Gly Gln Pro Arg Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr
1010 1015 1020
Pro Leu Arg Asn Leu Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val
1025 1030 1035 1040
Ala Ile Lys Gly Asn Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr
1045 1050 1055
Thr Leu Gln Pro Gly Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr
1060 1065 1070
Glu Thr Thr Ile Val Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe
1075 1080 1085
Lys Leu Gly Val Arg Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val
1090 1095 1100
Thr Ser Asp Ser Gly Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val
1105 1110 1115 1120
Glu Tyr Val Tyr Thr Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp
1125 1130 1135
Ala Pro Ile Val Asn Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn

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          1140                1145                1150
Leu His Leu Glu Ala Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp
        1155                1160                1165
Glu Arg Ser Thr Thr Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr
    1170                1175                1180
Pro Thr Asn Gly Gln Gln Gly Asn Ser Leu Glu Glu Val Val His Ala
1185                1190                1195                1200
Asp Gln Ser Ser Cys Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr
                1205                1210                1215
Asn Val Ser Val Tyr Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile
            1220                1225                1230
Ser Asp Thr Ile Ile Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe
        1235                1240                1245
Thr Asn Ile Gly Pro Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro
    1250                1255                1260
Ser Ile Asp Leu Thr Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn
1265                1270                1275                1280
Glu Glu Asp Val Ala Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val
                1285                1290                1295
Val Leu Thr Asn Leu Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser
            1300                1305                1310
Ser Val Tyr Glu Gln His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys
        1315                1320                1325
Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala
    1330                1335                1340
Asn Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly
1345                1350                1355                1360
Tyr Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu
                1365                1370                1375
Asp Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr
            1380                1385                1390
Pro Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu
        1395                1400                1405
Glu Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro
    1410                1415                1420
Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
1425                1430                1435                1440
Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly
                1445                1450                1455
Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser
            1460                1465                1470
Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
        1475                1480                1485
Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser
    1490                1495                1500
Lys Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
1505                1510                1515                1520
Met Gln Val Thr Asp Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu
                1525                1530                1535
Pro Ser Ser Ser Pro Val Thr Gly Tyr Arg Val Thr Thr Thr Pro Lys
            1540                1545                1550
Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr
        1555                1560                1565
```

Glu Met Thr Ile Glu Gly Leu Gln Pro Thr Val Glu Tyr Val Val Ser
1570 1575 1580
Val Tyr Ala Gln Asn Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr
1585 1590 1595 1600
Ala Val Thr Asn Ile Asp Arg Pro Lys Gly Leu Ala Phe Thr Asp Val
1605 1610 1615
Asp Val Asp Ser Ile Lys Ile Ala Trp Glu Ser Pro Gln Gly Gln Val
1620 1625 1630
Ser Arg Tyr Arg Val Thr Tyr Ser Ser Pro Glu Asp Gly Ile His Glu
1635 1640 1645
Leu Phe Pro Ala Pro Asp Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly
1650 1655 1660
Leu Arg Pro Gly Ser Glu Tyr Thr Val Ser Val Val Ala Leu His Asp
1665 1670 1675 1680
Asp Met Glu Ser Gln Pro Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro
1685 1690 1695
Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser
1700 1705 1710
Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg
1715 1720 1725
Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala
1730 1735 1740
Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys
1745 1750 1755 1760
Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro
1765 1770 1775
Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg
1780 1785 1790
Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg
1795 1800 1805
Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala
1810 1815 1820
Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser
1825 1830 1835 1840
Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu
1845 1850 1855
Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala
1860 1865 1870
Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr
1875 1880 1885
Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr
1890 1895 1900
Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val
1905 1910 1915 1920
Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu
1925 1930 1935
Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn
1940 1945 1950
Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro
1955 1960 1965
Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu
1970 1975 1980
Asp Val Pro Ser Thr Val Gln Lys Thr Pro Phe Val Thr His Pro Gly

1985 1990 1995 2000
Tyr Asp Thr Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln
2005 2010 2015
Pro Ser Val Gly Gln Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg
2020 2025 2030
Thr Thr Pro Pro Thr Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro
2035 2040 2045
Tyr Pro Pro Asn Val Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser
2050 2055 2060
Trp Ala Pro Phe Gln Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro
2065 2070 2075 2080
Val Gly Thr Asp Glu Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser
2085 2090 2095
Thr Ser Ala Thr Leu Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile
2100 2105 2110
Ile Val Glu Ala Leu Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu
2115 2120 2125
Val Val Thr Val Gly Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr
2130 2135 2140
Asp Asp Ser Cys Phe Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly
2145 2150 2155 2160
Asp Glu Trp Glu Arg Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln
2165 2170 2175
Cys Leu Gly Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp
2180 2185 2190
Cys His Asp Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg
2195 2200 2205
Gln Gly Glu Asn Gly Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly
2210 2215 2220
Lys Gly Glu Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp
2225 2230 2235 2240
Gly Lys Thr Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly
2245 2250 2255
Ala Ile Cys Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys
2260 2265 2270
Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr
2275 2280 2285
Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn
2290 2295 2300
Thr Asn Val Asn Cys Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln
2305 2310 2315 2320
Ala Asp Arg Glu Asp Ser Arg Glu
2325

<210> 99
<211> 188
<212> PRT
<213> Homo sapiens

<400> 99
His Gln Thr His Lys Glu Gly Gly Ser Thr His Ala Ser Ala Asp Ala
1 5 10 15
Trp Glu Ile Ile Glu Leu Glu Thr Glu Ile Glu Lys Phe Lys Ala Glu

```
            20                  25                  30
Asn Ala Ser Leu Ala Lys Leu Arg Ile Glu Arg Glu Ser Ala Leu Glu
        35                  40                  45
Lys Leu Arg Lys Glu Ile Ala Asp Phe Glu Gln Gln Lys Ala Lys Glu
    50                  55                  60
Leu Ala Arg Ile Glu Glu Phe Lys Lys Glu Glu Met Arg Lys Leu Gln
65                  70                  75                  80
Lys Glu Arg Lys Val Phe Glu Lys Tyr Thr Thr Ala Ala Arg Thr Phe
                85                  90                  95
Pro Asp Lys Lys Glu Arg Glu Glu Ile Gln Thr Leu Lys Gln Gln Ile
            100                 105                 110
Ala Asp Leu Arg Glu Asp Leu Lys Arg Lys Glu Thr Lys Trp Ser Ser
        115                 120                 125
Thr His Ser Arg Leu Arg Ser Gln Ile Gln Met Leu Val Arg Glu Asn
    130                 135                 140
Thr Asp Leu Arg Glu Glu Ile Lys Val Met Glu Arg Phe Arg Leu Asp
145                 150                 155                 160
Ala Trp Lys Arg Ala Glu Ala Ile Glu Ser Ser Leu Glu Val Glu Lys
                165                 170                 175
Lys Asp Lys Leu Ala Asn Thr Ser Val Arg Phe Gln
            180                 185
```

<210> 100
<211> 284
<212> PRT
<213> Homo sapiens

<400> 100

```
Met Glu Pro Gly Asn Tyr Ala Thr Leu Asp Gly Ala Lys Asp Ile Glu
 1              5                   10                  15
Gly Leu Leu Gly Ala Gly Gly Gly Arg Asn Leu Val Ala His Ser Pro
            20                  25                  30
Leu Thr Ser His Pro Ala Ala Pro Thr Leu Met Pro Ala Val Asn Tyr
        35                  40                  45
Ala Pro Leu Asp Leu Pro Gly Ser Ala Glu Pro Pro Lys Gln Cys His
    50                  55                  60
Pro Cys Pro Gly Val Pro Gln Gly Thr Ser Pro Ala Pro Val Pro Tyr
65                  70                  75                  80
Gly Tyr Phe Gly Gly Gly Tyr Tyr Ser Cys Arg Val Ser Arg Ser Ser
                85                  90                  95
Leu Lys Pro Cys Ala Gln Ala Ala Thr Leu Ala Ala Tyr Pro Ala Glu
            100                 105                 110
Thr Pro Thr Ala Gly Glu Glu Tyr Pro Ser Arg Pro Thr Glu Phe Ala
        115                 120                 125
Phe Tyr Pro Gly Tyr Pro Gly Thr Tyr His Ala Met Ala Ser Tyr Leu
    130                 135                 140
Asp Val Ser Val Val Gln Thr Leu Gly Ala Pro Gly Glu Pro Arg His
145                 150                 155                 160
Asp Ser Leu Leu Pro Val Asp Ser Tyr Gln Ser Trp Ala Leu Ala Gly
                165                 170                 175
Gly Trp Asn Ser Gln Met Cys Cys Gln Gly Glu Gln Asn Pro Pro Gly
            180                 185                 190
Pro Phe Trp Lys Ala Ala Phe Ala Asp Ser Ser Gly Gln His Pro Pro
```

```
        195                 200                 205
Asp Ala Cys Ala Phe Arg Arg Gly Arg Lys Lys Arg Ile Pro Tyr Ser
    210                 215                 220
Lys Gly Gln Leu Arg Glu Leu Glu Arg Glu Tyr Ala Ala Asn Lys Phe
225                 230                 235                 240
Ile Thr Lys Asp Lys Arg Arg Lys Ile Ser Ala Ala Thr Ser Leu Ser
                245                 250                 255
Glu Arg Gln Ile Thr Ile Trp Phe Gln Asn Arg Arg Val Lys Glu Lys
            260                 265                 270
Lys Val Leu Ala Lys Val Lys Asn Ser Ala Thr Pro
        275                 280
```

<210> 101
<211> 676
<212> PRT
<213> Homo sapiens

<400> 101

```
Met Asp Lys Tyr Asp Asp Leu Gly Leu Glu Ala Ser Lys Phe Ile Glu
 1               5                  10                  15
Asp Leu Asn Met Tyr Glu Ala Ser Lys Asp Gly Leu Phe Arg Val Asp
            20                  25                  30
Lys Gly Ala Gly Asn Asn Pro Glu Phe Glu Glu Thr Arg Arg Val Phe
        35                  40                  45
Ala Thr Lys Met Ala Lys Ile His Leu Gln Gln Gln Gln Gln Gln Leu
    50                  55                  60
Leu Gln Glu Glu Thr Leu Pro Arg Gly Ser Arg Gly Pro Val Asn Gly
65                  70                  75                  80
Gly Gly Arg Leu Gly Pro Gln Ala Arg Trp Glu Val Val Gly Ser Lys
                85                  90                  95
Leu Thr Val Asp Gly Ala Ala Lys Pro Pro Leu Ala Ala Ser Thr Gly
            100                 105                 110
Ala Pro Gly Ala Val Thr Thr Leu Ala Ala Gly Gln Pro Pro Tyr Pro
        115                 120                 125
Pro Gln Glu Gln Arg Ser Arg Pro Tyr Leu His Gly Thr Arg His Gly
    130                 135                 140
Ser Gln Asp Cys Gly Ser Arg Glu Ser Leu Ala Thr Ser Glu Met Ser
145                 150                 155                 160
Ala Phe His Gln Pro Gly Pro Cys Glu Asp Pro Ser Cys Leu Thr His
                165                 170                 175
Gly Asp Tyr Tyr Asp Asn Leu Ser Leu Ala Ser Pro Lys Trp Gly Asp
            180                 185                 190
Lys Pro Gly Val Ser Pro Ser Ile Gly Leu Ser Val Gly Ser Gly Trp
        195                 200                 205
Pro Ser Ser Pro Gly Ser Asp Pro Pro Leu Pro Lys Pro Cys Gly Asp
    210                 215                 220
His Pro Leu Asn His Arg Gln Leu Ser Leu Ser Ser Ser Arg Ser Ser
225                 230                 235                 240
Glu Gly Ser Leu Gly Gly Gln Asn Ser Gly Ile Gly Gly Arg Ser Ser
                245                 250                 255
Glu Lys Pro Thr Gly Leu Trp Ser Thr Ala Ser Ser Gln Arg Val Ser
            260                 265                 270
Pro Gly Leu Pro Ser Pro Asn Leu Glu Asn Gly Ala Pro Ala Val Gly
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        275                 280                 285
Pro Val Gln Pro Arg Thr Pro Ser Val Ser Ala Pro Leu Ala Leu Ser
    290                 295                 300
Cys Pro Arg Gln Gly Gly Leu Pro Arg Ser Asn Ser Gly Leu Gly Gly
305                 310                 315                 320
Glu Val Ser Gly Val Met Ser Lys Pro Asn Val Asp Pro Gln Pro Trp
                325                 330                 335
Phe Gln Asp Gly Pro Lys Ser Tyr Leu Ser Ser Ser Ala Pro Ser Ser
            340                 345                 350
Ser Pro Ala Gly Leu Asp Gly Ser Gln Gln Gly Ala Val Pro Gly Leu
        355                 360                 365
Gly Pro Lys Pro Gly Cys Thr Asp Leu Gly Thr Gly Pro Lys Leu Ser
    370                 375                 380
Pro Thr Ser Leu Val His Pro Val Met Ser Thr Leu Pro Glu Leu Ser
385                 390                 395                 400
Cys Lys Glu Gly Pro Leu Gly Trp Ser Ser Asp Gly Ser Leu Gly Ser
                405                 410                 415
Val Leu Leu Asp Ser Pro Ser Ser Pro Arg Val Arg Leu Pro Cys Gln
            420                 425                 430
Pro Leu Val Pro Gly Pro Glu Leu Arg Pro Ser Ala Ala Glu Leu Lys
        435                 440                 445
Leu Glu Ala Leu Thr Gln Arg Leu Glu Arg Glu Met Asp Ala His Pro
    450                 455                 460
Lys Ala Asp Tyr Phe Gly Ala Cys Val Lys Cys Ser Lys Gly Val Phe
465                 470                 475                 480
Gly Ala Gly Gln Ala Cys Gln Ala Met Gly Asn Leu Tyr His Asp Thr
                485                 490                 495
Cys Phe Thr Cys Ala Ala Cys Ser Arg Lys Leu Arg Gly Lys Ala Phe
            500                 505                 510
Tyr Phe Val Asn Gly Lys Val Phe Cys Glu Glu Asp Phe Leu Tyr Ser
        515                 520                 525
Gly Phe Gln Gln Ser Ala Asp Arg Cys Phe Leu Cys Gly His Leu Ile
    530                 535                 540
Met Asp Met Ile Leu Gln Ala Leu Gly Lys Ser Tyr His Pro Gly Cys
545                 550                 555                 560
Phe Arg Cys Val Ile Cys Asn Glu Cys Leu Asp Gly Val Pro Phe Thr
                565                 570                 575
Val Asp Ser Glu Asn Lys Ile Tyr Cys Val Arg Asp Tyr His Lys Val
            580                 585                 590
Leu Ala Pro Lys Cys Ala Ala Cys Gly Leu Pro Ile Leu Pro Pro Glu
        595                 600                 605
Gly Ser Asp Glu Thr Ile Arg Val Val Ser Met Asp Arg Asp Tyr His
    610                 615                 620
Val Glu Cys Tyr His Cys Glu Asp Cys Gly Leu Glu Leu Asn Asp Glu
625                 630                 635                 640
Asp Gly His Arg Cys Tyr Pro Leu Glu Asp His Leu Phe Cys His Ser
                645                 650                 655
Cys His Val Lys Arg Leu Glu Lys Arg Pro Ser Ser Thr Ala Leu His
            660                 665                 670
Gln His His Phe
        675
```

<210> 102

<211> 296
<212> PRT
<213> Homo sapiens

<400> 102
Ser Thr Gly Ser Glu Phe Pro Leu Cys Thr Lys Ala Ser Pro Cys Ser
1   5   10   15
Ala Ala Arg Ala Gly Gly Arg Ala Leu Gly Trp Arg Leu Gln Gln Gln
            20   25   30
Arg Glu Thr Arg Gly Asn Pro Gly Asn Pro Gly Leu Gly Val Ala Ala
        35   40   45
Thr Met Thr Gly Ser Asn Met Ser Asp Ala Leu Ala Asn Ala Val Cys
    50   55   60
Gln Arg Cys Gln Ala Arg Phe Ser Pro Ala Glu Arg Ile Val Asn Ser
65   70   75   80
Asn Gly Glu Leu Tyr His Glu His Cys Phe Val Cys Ala Gln Cys Phe
                85   90   95
Arg Pro Phe Pro Glu Gly Leu Phe Tyr Glu Phe Glu Gly Arg Lys Tyr
            100   105   110
Cys Glu His Asp Phe Gln Met Leu Phe Ala Pro Cys Cys Gly Ser Cys
        115   120   125
Gly Glu Phe Ile Ile Gly Arg Val Ile Lys Ala Met Asn Asn Asn Trp
    130   135   140
His Pro Gly Cys Phe Arg Cys Glu Leu Cys Asp Val Glu Leu Ala Asp
145   150   155   160
Leu Gly Phe Val Lys Asn Ala Gly Arg His Leu Cys Arg Pro Cys His
                165   170   175
Asn Arg Glu Lys Ala Lys Gly Leu Gly Lys Tyr Ile Cys Gln Arg Cys
            180   185   190
His Leu Val Ile Asp Glu Gln Pro Leu Met Phe Arg Ser Asp Ala Tyr
        195   200   205
His Pro Asp His Phe Asn Cys Thr His Cys Gly Lys Glu Leu Thr Ala
    210   215   220
Glu Ala Arg Glu Leu Lys Gly Glu Leu Tyr Cys Leu Pro Cys His Asp
225   230   235   240
Lys Met Gly Val Pro Ile Cys Gly Ala Cys Arg Arg Pro Ile Glu Gly
                245   250   255
Arg Val Val Asn Ala Leu Gly Lys Gln Trp His Val Glu His Phe Val
            260   265   270
Cys Ala Lys Cys Glu Lys Pro Phe Leu Gly His Arg His Tyr Glu Lys
        275   280   285
Lys Gly Leu Ala Tyr Cys Glu Leu
    290   295

<210> 103
<211> 500
<212> PRT
<213> Homo sapiens

<400> 103
Met Gly Ile Gly Leu Ser Ala Gln Gly Val Asn Met Asn Arg Leu Pro
1   5   10   15
Gly Trp Asp Lys His Ser Tyr Gly Tyr His Gly Asp Asp Gly His Ser

20 25 30
Phe Cys Ser Ser Gly Thr Gly Gln Pro Tyr Gly Pro Thr Phe Thr Thr
35 40 45
Gly Asp Val Ile Gly Cys Cys Val Asn Leu Ile Asn Asn Thr Cys Phe
50 55 60
Tyr Thr Lys Asn Gly His Ser Leu Gly Ile Ala Phe Thr Asp Leu Pro
65 70 75 80
Pro Asn Leu Tyr Pro Thr Val Gly Leu Gln Thr Pro Gly Glu Val Val
85 90 95
Asp Ala Asn Phe Gly Gln His Pro Phe Val Phe Asp Ile Glu Asp Tyr
100 105 110
Met Arg Glu Trp Arg Thr Lys Ile Gln Ala Gln Ile Asp Arg Phe Pro
115 120 125
Ile Gly Asp Arg Glu Gly Glu Trp Gln Thr Met Ile Gln Lys Met Val
130 135 140
Ser Ser Tyr Leu Val His His Gly Tyr Cys Ala Thr Ala Glu Ala Phe
145 150 155 160
Ala Arg Ser Thr Asp Gln Thr Val Leu Glu Glu Leu Ala Ser Ile Lys
165 170 175
Asn Arg Gln Arg Ile Gln Lys Leu Val Leu Ala Gly Arg Met Gly Glu
180 185 190
Ala Ile Glu Thr Thr Gln Gln Leu Tyr Pro Ser Leu Leu Glu Arg Asn
195 200 205
Pro Asn Leu Leu Phe Thr Leu Lys Val Arg Gln Phe Ile Glu Met Val
210 215 220
Asn Gly Thr Asp Ser Glu Val Arg Cys Leu Gly Gly Arg Ser Pro Lys
225 230 235 240
Ser Gln Asp Ser Tyr Pro Val Ser Pro Arg Pro Phe Ser Ser Pro Ser
245 250 255
Met Ser Pro Ser His Gly Met Asn Ile His Asn Leu Ala Ser Gly Lys
260 265 270
Gly Ser Thr Ala His Phe Ser Gly Phe Glu Ser Cys Ser Asn Gly Val
275 280 285
Ile Ser Asn Lys Ala His Gln Ser Tyr Cys His Ser Asn Lys His Gln
290 295 300
Ser Ser Asn Leu Asn Val Pro Glu Leu Asn Ser Ile Asn Met Ser Arg
305 310 315 320
Ser Gln Gln Val Asn Asn Phe Thr Ser Asn Asp Val Asp Met Glu Thr
325 330 335
Asp His Tyr Ser Asn Gly Val Gly Glu Thr Ser Ser Asn Gly Phe Leu
340 345 350
Asn Gly Ser Ser Lys His Asp His Glu Met Glu Asp Cys Asp Thr Glu
355 360 365
Met Glu Val Asp Ser Ser Gln Leu Arg Arg Gln Leu Cys Gly Gly Ser
370 375 380
Gln Ala Ala Ile Glu Arg Met Ile His Phe Gly Arg Glu Leu Gln Ala
385 390 395 400
Met Ser Glu Gln Leu Arg Arg Asp Cys Gly Lys Asn Thr Ala Asn Lys
405 410 415
Lys Met Leu Lys Asp Ala Phe Ser Leu Leu Ala Tyr Ser Asp Pro Trp
420 425 430
Asn Ser Pro Val Gly Asn Gln Leu Asp Pro Ile Gln Arg Glu Pro Val
435 440 445

Cys Ser Ala Leu Asn Ser Ala Ile Leu Glu Thr His Asn Leu Pro Lys
450 455 460
Gln Pro Pro Leu Ala Leu Ala Met Gly Gln Ala Thr Gln Cys Leu Gly
465 470 475 480
Leu Met Ala Arg Ser Gly Ile Gly Ser Cys Ala Phe Ala Thr Val Glu
485 490 495
Asp Tyr Leu His
500

<210> 104
<211> 387
<212> PRT
<213> Homo sapiens

<400> 104
Met Ala Thr Ser Gly Val Leu Pro Gly Gly Gly Phe Val Ala Ser Ala
1 5 10 15
Ala Ala Val Ala Gly Pro Glu Met Gln Thr Gly Arg Asn Asn Phe Val
20 25 30
Ile Arg Arg Asn Pro Ala Asp Pro Gln Arg Ile Pro Ser Asn Pro Ser
35 40 45
His Arg Ile Gln Cys Ala Ala Gly Tyr Glu Gln Ser Glu His Asn Val
50 55 60
Cys Gln Asp Ile Asp Glu Cys Thr Ala Gly Thr His Asn Cys Arg Ala
65 70 75 80
Asp Gln Val Cys Ile Asn Leu Arg Gly Ser Phe Ala Cys Gln Cys Pro
85 90 95
Pro Gly Tyr Gln Lys Arg Gly Glu Gln Cys Val Asp Ile Asp Glu Cys
100 105 110
Thr Ile Pro Pro Tyr Cys His Gln Arg Cys Val Asn Thr Pro Gly Ser
115 120 125
Phe Tyr Cys Gln Cys Ser Pro Gly Phe Gln Leu Ala Ala Asn Asn Tyr
130 135 140
Thr Cys Val Asp Ile Asn Glu Cys Asp Ala Ser Asn Gln Cys Ala Gln
145 150 155 160
Gln Cys Tyr Asn Ile Leu Gly Ser Phe Ile Cys Gln Cys Asn Gln Gly
165 170 175
Tyr Glu Leu Ser Ser Asp Arg Leu Asn Cys Glu Asp Ile Asp Glu Cys
180 185 190
Arg Thr Ser Ser Tyr Leu Cys Gln Tyr Gln Cys Val Asn Glu Pro Gly
195 200 205
Lys Phe Ser Cys Met Cys Pro Gln Gly Tyr Gln Val Val Arg Ser Arg
210 215 220
Thr Cys Gln Asp Ile Asn Glu Cys Glu Thr Thr Asn Glu Cys Arg Glu
225 230 235 240
Asp Glu Met Cys Trp Asn Tyr His Gly Gly Phe Arg Cys Tyr Pro Arg
245 250 255
Asn Pro Cys Gln Asp Pro Tyr Ile Leu Thr Pro Glu Asn Arg Cys Val
260 265 270
Cys Pro Val Ser Asn Ala Met Cys Arg Glu Leu Pro Gln Ser Ile Val
275 280 285
Tyr Lys Tyr Met Ser Ile Arg Ser Asp Arg Ser Val Pro Ser Asp Ile
290 295 300

Phe Gln Ile Gln Ala Thr Thr Ile Tyr Ala Asn Thr Ile Asn Thr Phe
305 310 315 320
Arg Ile Lys Ser Gly Asn Glu Asn Gly Glu Phe Tyr Leu Arg Gln Thr
325 330 335
Ser Pro Val Ser Ala Met Leu Val Leu Val Lys Ser Leu Ser Gly Pro
340 345 350
Arg Glu His Ile Val Asp Leu Glu Met Leu Thr Val Ser Ser Ile Gly
355 360 365
Thr Phe Arg Thr Ser Ser Val Leu Arg Leu Thr Ile Ile Val Gly Pro
370 375 380
Phe Ser Phe
385

<210> 105
<211> 531
<212> PRT
<213> Homo sapiens

<400> 105
Met Ser Lys Pro His Ser Glu Ala Gly Thr Ala Phe Ile Gln Thr Gln
1 5 10 15
Gln Leu His Ala Ala Met Ala Asp Thr Phe Leu Glu His Met Cys Arg
20 25 30
Leu Asp Ile Asp Ser Pro Pro Ile Thr Ala Arg Asn Thr Gly Ile Ile
35 40 45
Cys Thr Ile Gly Pro Ala Ser Arg Ser Val Glu Thr Leu Lys Glu Met
50 55 60
Ile Lys Ser Gly Met Asn Val Ala Arg Leu Asn Phe Ser His Gly Thr
65 70 75 80
His Glu Tyr His Ala Glu Thr Ile Lys Asn Val Arg Thr Ala Thr Glu
85 90 95
Ser Phe Ala Ser Asp Pro Tyr Leu Tyr Arg Pro Val Ala Val Ala Leu
100 105 110
Asp Thr Lys Gly Pro Glu Ile Arg Thr Gly Leu Ile Lys Gly Ser Gly
115 120 125
Thr Ala Glu Leu Glu Leu Lys Lys Gly Ala Thr Leu Lys Ile Thr Leu
130 135 140
Asp Asn Ala Tyr Met Glu Lys Cys Asp Glu Asn Ile Leu Trp Leu Asp
145 150 155 160
Tyr Lys Asn Ile Cys Lys Val Val Glu Val Gly Ser Lys Ile Tyr Val
165 170 175
Asp Asp Gly Leu Ile Ser Leu Gln Val Lys Gln Lys Gly Ala Asp Phe
180 185 190
Leu Val Thr Glu Val Glu Asn Gly Gly Ser Leu Gly Ser Lys Lys Gly
195 200 205
Val Asn Leu Pro Gly Ala Ala Val Asp Leu Pro Ala Val Ser Glu Lys
210 215 220
Asp Ile Gln Asp Leu Lys Phe Gly Val Glu Gln Asp Val Asp Met Val
225 230 235 240
Phe Ala Ser Phe Ile Arg Lys Ala Ser Asp Val His Glu Val Arg Lys
245 250 255
Val Leu Gly Glu Lys Gly Lys Asn Ile Lys Ile Ile Ser Lys Ile Glu
260 265 270

Asn His Glu Gly Val Arg Arg Phe Asp Glu Ile Leu Glu Ala Ser Asp
275 280 285
Gly Ile Met Val Ala Arg Gly Asp Leu Gly Ile Glu Ile Pro Ala Glu
290 295 300
Lys Val Phe Leu Ala Gln Lys Met Met Ile Gly Arg Cys Asn Arg Ala
305 310 315 320
Gly Lys Pro Val Ile Cys Ala Thr Gln Met Leu Glu Ser Met Ile Lys
325 330 335
Lys Pro Arg Pro Thr Arg Ala Glu Gly Ser Asp Val Ala Asn Ala Val
340 345 350
Leu Asp Gly Ala Asp Cys Ile Met Leu Ser Gly Glu Thr Ala Lys Gly
355 360 365
Asp Tyr Pro Leu Glu Ala Val Arg Met Gln His Leu Ile Ala Arg Glu
370 375 380
Ala Glu Ala Ala Ile Tyr His Leu Gln Leu Phe Glu Glu Leu Arg Arg
385 390 395 400
Leu Ala Pro Ile Thr Ser Asp Pro Thr Glu Ala Thr Ala Val Gly Ala
405 410 415
Val Glu Ala Ser Phe Lys Cys Cys Ser Gly Ala Ile Ile Val Leu Thr
420 425 430
Lys Ser Gly Arg Ser Ala His Gln Val Ala Arg Tyr Arg Pro Arg Ala
435 440 445
Pro Ile Ile Ala Val Thr Arg Asn Pro Gln Thr Ala Arg Gln Ala His
450 455 460
Leu Tyr Arg Gly Ile Phe Pro Val Leu Cys Lys Asp Pro Val Gln Glu
465 470 475 480
Ala Trp Ala Glu Asp Val Asp Leu Arg Val Asn Phe Ala Met Asn Val
485 490 495
Gly Lys Ala Arg Gly Phe Phe Lys Lys Gly Asp Val Val Ile Val Leu
500 505 510
Thr Gly Trp Arg Pro Gly Ser Gly Phe Thr Asn Thr Met Arg Val Val
515 520 525
Pro Val Pro
530

<210> 106
<211> 480
<212> PRT
<213> Homo sapiens

<400> 106
Met Ala Ala Arg Cys Ser Thr Arg Trp Leu Leu Val Val Val Gly Thr
1 5 10 15
Pro Arg Leu Pro Ala Ile Ser Gly Arg Gly Ala Arg Pro Pro Arg Glu
20 25 30
Gly Val Val Gly Ala Trp Leu Ser Arg Lys Leu Ser Val Pro Ala Phe
35 40 45
Ala Ser Ser Leu Thr Ser Cys Gly Pro Arg Ala Leu Leu Thr Leu Arg
50 55 60
Pro Gly Val Ser Leu Thr Gly Thr Lys His Asn Pro Phe Ile Cys Thr
65 70 75 80
Ala Ser Phe His Thr Ser Ala Pro Leu Ala Lys Glu Asp Tyr Tyr Gln
85 90 95

Ile Leu Gly Val Pro Arg Asn Ala Ser Gln Lys Glu Ile Lys Lys Ala
100 105 110
Tyr Tyr Gln Leu Ala Lys Lys Tyr His Pro Asp Thr Asn Lys Asp Asp
115 120 125
Pro Lys Ala Lys Glu Lys Phe Ser Gln Leu Ala Glu Ala Tyr Glu Val
130 135 140
Leu Ser Asp Glu Val Lys Arg Lys Gln Tyr Asp Ala Tyr Gly Ser Ala
145 150 155 160
Gly Phe Asp Pro Gly Ala Ser Gly Ser Gln His Ser Tyr Trp Lys Gly
165 170 175
Gly Pro Thr Val Asp Pro Glu Glu Leu Phe Arg Lys Ile Phe Gly Glu
180 185 190
Phe Ser Ser Ser Ser Phe Gly Asp Phe Gln Thr Val Phe Asp Gln Pro
195 200 205
Gln Glu Tyr Phe Met Glu Leu Thr Phe Asn Gln Ala Ala Lys Gly Val
210 215 220
Asn Lys Glu Phe Thr Val Asn Ile Met Asp Thr Cys Glu Arg Cys Asn
225 230 235 240
Gly Lys Gly Asn Glu Pro Gly Thr Lys Val Gln His Cys His Tyr Cys
245 250 255
Gly Gly Ser Gly Met Glu Thr Ile Asn Thr Gly Pro Phe Val Met Arg
260 265 270
Ser Thr Cys Arg Arg Cys Gly Gly Arg Gly Ser Ile Ile Ile Ser Pro
275 280 285
Cys Val Val Cys Arg Gly Ala Gly Gln Ala Lys Gln Lys Lys Arg Val
290 295 300
Met Ile Pro Val Pro Ala Gly Val Glu Asp Gly Gln Thr Val Arg Met
305 310 315 320
Pro Val Gly Lys Arg Glu Ile Phe Ile Thr Phe Arg Val Gln Lys Ser
325 330 335
Pro Val Phe Arg Arg Asp Gly Ala Asp Ile His Ser Asp Leu Phe Ile
340 345 350
Ser Ile Ala Gln Ala Leu Leu Gly Gly Thr Ala Arg Ala Gln Gly Leu
355 360 365
Tyr Glu Thr Ile Asn Val Thr Ile Pro Pro Gly Thr Gln Thr Asp Gln
370 375 380
Lys Ile Arg Met Gly Gly Lys Gly Ile Pro Arg Ile Asn Ser Tyr Gly
385 390 395 400
Tyr Gly Asp His Tyr Ile His Ile Lys Ile Arg Val Pro Lys Arg Leu
405 410 415
Thr Ser Arg Gln Gln Ser Leu Ile Leu Ser Tyr Ala Glu Asp Glu Thr
420 425 430
Asp Val Glu Gly Thr Val Asn Gly Val Thr Leu Thr Ser Ser Gly Gly
435 440 445
Ser Thr Met Asp Ser Ser Ala Gly Ser Lys Ala Arg Arg Glu Ala Gly
450 455 460
Glu Asp Glu Glu Gly Phe Leu Ser Lys Leu Lys Lys Met Phe Thr Ser
465 470 475 480

<210> 107
<211> 572
<212> PRT
<213> Homo sapiens

<400> 107

Met Ala Ala Pro Arg Pro Ser Pro Ala Ile Ser Val Ser Val Ser Ala
1   5   10   15
Pro Ala Phe Tyr Ala Pro Gln Lys Lys Phe Gly Pro Val Val Ala Pro
            20   25   30
Lys Pro Lys Val Asn Pro Phe Arg Pro Gly Asp Ser Glu Pro Pro Pro
        35   40   45
Ala Pro Gly Ala Gln Arg Ala Gln Met Gly Arg Val Gly Glu Ile Pro
    50   55   60
Pro Pro Pro Pro Glu Asp Phe Pro Leu Pro Pro Pro Pro Leu Ala Gly
65   70   75   80
Asp Gly Asp Asp Ala Glu Gly Ala Leu Gly Gly Ala Phe Pro Pro Pro
                85   90   95
Pro Pro Pro Ile Glu Glu Ser Phe Pro Pro Ala Pro Leu Glu Glu Glu
            100   105   110
Ile Phe Pro Ser Pro Pro Pro Pro Pro Glu Glu Glu Gly Gly Pro Glu
        115   120   125
Ala Pro Ile Pro Pro Pro Pro Gln Pro Arg Glu Lys Val Ser Ser Ile
    130   135   140
Asp Leu Glu Ile Asp Ser Leu Ser Ser Leu Leu Asp Asp Met Thr Lys
145   150   155   160
Asn Asp Pro Phe Lys Ala Arg Val Ser Ser Gly Tyr Val Pro Pro Pro
                165   170   175
Val Ala Thr Pro Phe Ser Ser Lys Ser Ser Thr Lys Pro Ala Ala Gly
            180   185   190
Gly Thr Ala Pro Leu Pro Pro Trp Lys Ser Pro Ser Ser Ser Gln Pro
        195   200   205
Leu Pro Gln Val Pro Ala Pro Ala Gln Ser Gln Thr Gln Phe His Val
    210   215   220
Gln Pro Gln Pro Gln Pro Lys Pro Gln Val Gln Leu His Val Gln Ser
225   230   235   240
Gln Thr Gln Pro Val Ser Leu Ala Asn Thr Gln Pro Arg Gly Pro Pro
                245   250   255
Ala Ser Ser Pro Ala Pro Ala Pro Lys Phe Ser Pro Val Thr Pro Lys
            260   265   270
Phe Thr Pro Val Ala Ser Lys Phe Ser Pro Gly Ala Pro Gly Gly Ser
        275   280   285
Gly Ser Gln Pro Asn Gln Lys Leu Gly His Pro Glu Ala Leu Ser Ala
    290   295   300
Gly Thr Gly Ser Pro Gln Pro Pro Ser Phe Thr Tyr Ala Gln Gln Arg
305   310   315   320
Glu Lys Pro Arg Val Gln Glu Lys Gln His Pro Val Pro Pro Pro Ala
                325   330   335
Gln Asn Gln Asn Gln Val Arg Ser Pro Gly Ala Pro Gly Pro Leu Thr
            340   345   350
Leu Lys Glu Val Glu Glu Leu Glu Gln Leu Thr Gln Gln Leu Met Gln
        355   360   365
Asp Met Glu His Pro Gln Arg Gln Asn Val Ala Val Asn Glu Leu Cys
    370   375   380
Gly Arg Cys His Gln Pro Leu Ala Arg Ala Gln Pro Ala Val Arg Ala
385   390   395   400
Leu Gly Gln Leu Phe His Ile Ala Cys Phe Thr Cys His Gln Cys Ala
                405   410   415

Gln Gln Leu Gln Gly Gln Gln Phe Tyr Ser Leu Glu Gly Ala Pro Tyr
420 425 430
Cys Glu Gly Cys Tyr Thr Asp Thr Leu Glu Lys Cys Asn Thr Cys Gly
435 440 445
Glu Pro Ile Thr Asp Arg Met Leu Arg Ala Thr Gly Lys Ala Tyr His
450 455 460
Pro His Cys Phe Thr Cys Val Val Cys Ala Arg Pro Leu Glu Gly Thr
465 470 475 480
Ser Phe Ile Val Asp Gln Ala Asn Arg Pro His Cys Val Pro Asp Tyr
485 490 495
His Lys Gln Tyr Ala Pro Arg Cys Ser Val Cys Ser Glu Pro Ile Met
500 505 510
Pro Glu Pro Gly Arg Asp Glu Thr Val Arg Val Val Ala Leu Asp Lys
515 520 525
Asn Phe His Met Lys Cys Tyr Lys Cys Glu Asp Cys Gly Lys Pro Leu
530 535 540
Ser Ile Glu Ala Asp Asp Asn Gly Cys Phe Pro Leu Asp Gly His Val
545 550 555 560
Leu Cys Arg Lys Cys His Thr Ala Arg Ala Gln Thr
565 570

<210> 108
<211> 2861
<212> PRT
<213> Homo sapiens

<400> 108
Met Lys Ala Met Asp Val Leu Pro Ile Leu Lys Glu Lys Val Ala Tyr
1 5 10 15
Leu Ser Gly Gly Arg Asp Lys Arg Gly Gly Pro Ile Leu Thr Phe Pro
20 25 30
Ala Arg Ser Asn His Asp Arg Ile Arg Gln Glu Asp Leu Arg Arg Leu
35 40 45
Ile Ser Tyr Leu Ala Cys Ile Pro Ser Glu Glu Val Cys Lys Arg Gly
50 55 60
Phe Thr Val Ile Val Asp Met Arg Gly Ser Lys Trp Asp Ser Ile Lys
65 70 75 80
Pro Leu Leu Lys Ile Leu Gln Glu Ser Phe Pro Cys Cys Ile His Val
85 90 95
Ala Leu Ile Ile Lys Pro Asp Asn Phe Trp Gln Lys Gln Arg Thr Asn
100 105 110
Phe Gly Ser Ser Lys Phe Glu Phe Glu Thr Asn Met Val Ser Leu Glu
115 120 125
Gly Leu Thr Lys Val Val Asp Pro Ser Gln Leu Thr Pro Glu Phe Asp
130 135 140
Gly Cys Leu Glu Tyr Asn His Glu Glu Trp Ile Glu Ile Arg Val Ala
145 150 155 160
Phe Glu Asp Tyr Ile Ser Asn Ala Thr His Met Leu Ser Arg Leu Glu
165 170 175
Glu Leu Gln Asp Ile Leu Ala Lys Lys Glu Leu Pro Gln Asp Leu Glu
180 185 190
Gly Ala Arg Asn Met Ile Glu Glu His Ser Gln Leu Lys Lys Lys Val
195 200 205

Ile Lys Ala Pro Ile Glu Asp Leu Asp Leu Glu Gly Gln Lys Leu Leu
210 215 220
Gln Arg Ile Gln Ser Ser Glu Ser Phe Pro Lys Lys Asn Ser Gly Ser
225 230 235 240
Gly Asn Ala Asp Leu Gln Asn Leu Leu Pro Lys Val Ser Thr Met Leu
245 250 255
Asp Arg Leu His Ser Thr Arg Gln His Leu His Gln Met Trp His Val
260 265 270
Arg Lys Leu Lys Leu Asp Gln Cys Phe Gln Leu Arg Leu Phe Glu Gln
275 280 285
Asp Ala Glu Lys Met Phe Asp Trp Ile Thr His Asn Lys Gly Leu Phe
290 295 300
Leu Asn Ser Tyr Thr Glu Ile Gly Thr Ser His Pro His Ala Met Glu
305 310 315 320
Leu Gln Thr Gln His Asn His Phe Ala Met Asn Cys Met Asn Val Tyr
325 330 335
Val Asn Ile Asn Arg Ile Met Ser Val Ala Asn Arg Leu Val Glu Ser
340 345 350
Gly His Tyr Ala Ser Gln Gln Ile Arg Gln Ile Ala Ser Gln Leu Glu
355 360 365
Gln Glu Trp Lys Ala Phe Ala Ala Ala Leu Asp Glu Arg Ser Thr Leu
370 375 380
Leu Asp Met Ser Ser Ile Phe His Gln Lys Ala Glu Lys Tyr Met Ser
385 390 395 400
Asn Val Asp Ser Trp Cys Lys Ala Cys Gly Glu Val Asp Leu Pro Ser
405 410 415
Glu Leu Gln Asp Leu Glu Asp Ala Ile His His His Gln Gly Ile Tyr
420 425 430
Glu His Ile Thr Leu Ala Tyr Ser Glu Val Ser Gln Asp Gly Lys Ser
435 440 445
Leu Leu Asp Lys Leu Gln Arg Pro Leu Thr Pro Gly Ser Ser Asp Ser
450 455 460
Leu Thr Ala Ser Ala Asn Tyr Ser Lys Ala Val His His Val Leu Asp
465 470 475 480
Val Ile His Glu Val Leu His His Gln Arg His Val Arg Thr Ile Trp
485 490 495
Gln His Arg Lys Val Arg Leu His Gln Arg Leu Gln Leu Cys Val Phe
500 505 510
Gln Gln Glu Val Gln Gln Val Leu Asp Trp Ile Glu Asn His Gly Glu
515 520 525
Ala Phe Leu Ser Lys His Thr Gly Val Gly Lys Ser Leu His Arg Ala
530 535 540
Arg Ala Leu Gln Lys Arg His Glu Asp Phe Glu Glu Val Ala Gln Asn
545 550 555 560
Thr Tyr Thr Asn Ala Asp Lys Leu Leu Glu Ala Ala Glu Gln Leu Ala
565 570 575
Gln Thr Gly Glu Cys Asp Pro Glu Glu Ile Tyr Gln Ala Ala His Gln
580 585 590
Leu Glu Asp Arg Ile Gln Asp Phe Val Arg Arg Val Glu Gln Arg Lys
595 600 605
Ile Leu Leu Asp Met Ser Val Ser Phe His Thr His Val Lys Glu Leu
610 615 620
Trp Thr Trp Leu Glu Glu Leu Gln Lys Glu Leu Leu Asp Asp Val Tyr

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625                 630                 635                 640
Ala Glu Ser Val Glu Ala Val Gln Asp Leu Ile Lys Arg Phe Gly Gln
                645                 650                 655
Gln Gln Gln Thr Thr Leu Gln Val Thr Val Asn Val Ile Lys Glu Gly
            660                 665                 670
Glu Asp Leu Ile Gln Gln Leu Arg Asp Ser Ala Ile Ser Ser Asn Lys
        675                 680                 685
Thr Pro His Asn Ser Ser Ile Asn His Ile Glu Thr Val Leu Gln Gln
    690                 695                 700
Leu Asp Glu Ala Gln Ser Gln Met Glu Glu Leu Phe Gln Glu Arg Lys
705                 710                 715                 720
Ile Lys Leu Glu Leu Phe Leu His Val Arg Ile Phe Glu Arg Asp Ala
                725                 730                 735
Ile Asp Ile Ile Ser Asp Leu Glu Ser Trp Asn Asp Glu Leu Ser Gln
            740                 745                 750
Gln Met Asn Asp Phe Asp Thr Glu Asp Leu Thr Ile Ala Glu Gln Arg
        755                 760                 765
Leu Gln His His Ala Asp Lys Ala Leu Thr Met Asn Asn Leu Thr Phe
    770                 775                 780
Asp Val Ile His Gln Gly Gln Asp Leu Leu Gln Tyr Val Asn Glu Val
785                 790                 795                 800
Gln Ala Ser Gly Val Glu Leu Leu Cys Asp Arg Asp Val Asp Met Ala
                805                 810                 815
Thr Arg Val Gln Asp Leu Leu Glu Phe Leu His Glu Lys Gln Gln Glu
            820                 825                 830
Leu Asp Leu Ala Ala Glu Gln His Arg Lys His Leu Glu Gln Cys Val
        835                 840                 845
Gln Leu Arg His Leu Gln Ala Glu Val Lys Gln Val Leu Gly Trp Ile
    850                 855                 860
Arg Asn Gly Glu Ser Met Leu Asn Ala Gly Leu Ile Thr Ala Ser Ser
865                 870                 875                 880
Leu Gln Glu Ala Glu Gln Leu Gln Arg Glu His Glu Gln Phe Gln His
                885                 890                 895
Ala Ile Glu Lys Thr His Gln Ser Ala Leu Gln Val Gln Gln Lys Ala
            900                 905                 910
Glu Ala Met Leu Gln Ala Asn His Tyr Asp Met Asp Met Ile Arg Asp
        915                 920                 925
Cys Ala Glu Lys Val Ala Ser His Trp Gln Gln Leu Met Leu Lys Met
    930                 935                 940
Glu Asp Arg Leu Lys Leu Val Asn Ala Ser Val Ala Phe Tyr Lys Thr
945                 950                 955                 960
Ser Glu Gln Val Cys Ser Val Leu Glu Ser Leu Glu Gln Glu Tyr Lys
                965                 970                 975
Arg Glu Glu Asp Trp Cys Gly Gly Ala Asp Lys Leu Gly Pro Asn Ser
            980                 985                 990
Glu Thr Asp His Val Thr Pro Met Ile Ser Lys His Leu Glu Gln Lys
        995                 1000                1005
Glu Ala Phe Leu Lys Ala Cys Thr Leu Ala Arg Arg Asn Ala Asp Val
    1010                1015                1020
Phe Leu Lys Tyr Leu His Arg Asn Ser Val Asn Met Pro Gly Met Val
1025                1030                1035                1040
Thr His Ile Lys Ala Pro Glu Gln Gln Val Lys Asn Ile Leu Asn Glu
                1045                1050                1055
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<213> Homo sapiens

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16951

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/11 C12N5/10 C12N1/21 C07K14/705
C07K14/775 C07K14/47 C07K16/28 C12Q1/68 A61K49/00
G01N33/50 G01N33/53 G01N33/68 A01K67/027 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q A61K G01N A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, STRAND, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 46743 A (MERRIMAN TONY RAYMOND ;TWELLS REBECCA CHRISTINA JOAN (GB); COX ROG) 22 October 1998 (1998-10-22)	41,42
A	SeqIdNo.1: 99.6% identity in 1615 aa overlap with SeqIdNo.4 page 19, paragraph 3 -page 21, paragraph 1; figures 9,10,19,20; tables 3,5-7	1-8,22, 23, 26-40, 45-50, 55-69,74

X	US 5 691 153 A (GONG GUODONG ET AL) 25 November 1997 (1997-11-25) cited in the application	46,48
Y	claims 1-10; figures 1,2	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2001	11 07 2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Lonnoy, O

INTERNATIONAL SEARCH REPORT	International Application No PCT/US 00/16951

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOHNSON M ET AL: "Linkage of a gene causing high bone mass to human chromosome 11 (11q12-13)" AM J HUM GENET, vol. 60, no. 6, June 1997 (1997-06), pages 1326-1332, XP000992645 cited in the application	46,48
Y	figure 1; table 2	1-8

Y	KOLLER D ET AL: "Linkage of a QTL contributing to normal variation in bone mineral density to chromosome 11q12-13" J BONE MINER RES, vol. 13, no. 12, December 1998 (1998-12), pages 1903-1908, XP000992793 figure 1	1-8

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2001	11. 07. 2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Lonnoy, O

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WHYTE M P: "Searching for Gene Defects That Cause High Bone Mass" AM J HUM GENET, vol. 60, no. 6, June 1997 (1997-06), pages 1309-1311, XP000992644 ---	
A	KIM D ET AL: "A new low density lipoprotein receptor related protein, LRP5, is expressed in hepatocytes and adrenal cortex, and recognizes apolipoprotein E" J BIOCHEM, vol. 124, no. 6, 1 December 1998 (1998-12-01), pages 1072-1076, XP002165274 figures 1,2 ---	21
A	TROMMSDORFF M ET AL: "Interaction of cytosolic adaptor proteins with neuronal apolipoprotein E receptors and the amyloid precursor protein" JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 273, no. 50, 11 December 1998 (1998-12-11), pages 33556-33560, XP002165275 abstract ---	21
A	DATABASE EM_HTG [Online] E.B.I., Hinxton, U.K.; Accession Number: AC024123, 2 March 2000 (2000-03-02) COURSEAUX A ET AL: "Homo sapiens chromosome 11 clone bac67-m-5 map 11q13, *** SEQUENCING IN PROGRESS ***, 3 ordered pieces" XP002165276 abstract ---	51
A	SCHNEIDER G ET AL: "Formation of focal adhesions by osteoblasts adhering to different substrata" EXP CELL RES, vol. 214, no. 1, September 1994 (1994-09), pages 264-269, XP000992789 ---	
A	PAVALKO F ET AL: "Fluid shear-induced mechanical signaling in MC3T3-E1 osteoblasts requires cytoskeleton-integrin interactions." AM J PHYSIOL, vol. 275, no. 6 (Pt1), December 1998 (1998-12), pages C1591-C1601, XP000992787 ---	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16951

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 47529 A (BUCHANAN JOHN ;LUKE GEORGE P (US); BOHACEK REGINE (US); VU CHI B () 23 September 1999 (1999-09-23) ---	
A	WO 97 12903 A (PARA KIMBERLY SUZANNE ;SALTIEL ALAN ROBERT (US); SHAHRIPOUR AURASH) 10 April 1997 (1997-04-10) ---	
A	WO 99 09054 A (UNIV MONS HAINAUT ;FALMAGNE PAUL (BE); WATTIEZ RUDDY (BE); BERNARD) 25 February 1999 (1999-02-25) -----	

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 29-45, 78 and 91 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. [X] Claims Nos.: 43,44
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet invention 1.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: Claims 1-50 and 53-69 (all completely) and claims 51, 74, 75, 78 and 91 (all partially)

The HBM polynucleotide and HBM polypeptide variant of the polymorphic Zmax1 gene, said polynucleotide and polypeptide of SeqIdNo.2 and SeqIdNo.4 respectively, said polynucleotide comprising at least 15 contiguous nucleotides of SeqIdNo.2 wherein one of the at least 15 contiguous nucleotides is thymine at position 582; applications thereof.

2. Claims: Inventions 2 to 25: Claims 51, 52, 70, 72-74 (all partially)

A polymorphic variant of the Zmax 1 gene, wherein invention 2 is limited to SeqIdNo.9 wherein nucleotide 69169 is replaced by A,
invention 3 to SeqIdNo.9 wherein nucleotide 27402 is replaced by G,
invention 4 to SeqIdNo.9 wherein nucleotide 27841 is replaced by C,
invention 5 to SeqIdNo.9 wherein nucleotide 35600 is replaced by G,
invention 6 to SeqIdNo.9 wherein nucleotide 45619 is replaced by A,
invention 7 to SeqIdNo.9 wherein nucleotide 46018 is replaced by G,
invention 8 to SeqIdNo.9 wherein nucleotide 46093 is replaced by G,
invention 9 to SeqIdNo.9 wherein nucleotide 46190 is replaced by G,
invention 10 to SeqIdNo.9 wherein nucleotide 50993 is replaced by C,
invention 11 to SeqIdNo.9 wherein nucleotide 51124 is replaced by T,
invention 12 to SeqIdNo.9 wherein nucleotide 55461 is replaced by T,
invention 13 to SeqIdNo.9 wherein nucleotide 63645 is replaced by A,
invention 14 to SeqIdNo.9 wherein nucleotide 63646 is replaced by C,
invention 15 to SeqIdNo.9 wherein nucleotide 24809 is replaced by G,
invention 16 to SeqIdNo.9 wherein nucleotide 27837 is replaced by C,
invention 17 to SeqIdNo.9 wherein nucleotide 31485 is replaced by T,
invention 18 to SeqIdNo.9 wherein nucleotide 31683 is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

replaced by G,
invention 19 to SeqIdNo.9 wherein nucleotide 24808 is replaced by G,
invention 20 to SeqIdNo.8 wherein nucleotide 31340 is replaced by C,
invention 21 to SeqIdNo.8 wherein nucleotide 32538 is replaced by G,
invention 22 to SeqIdNo.8 wherein nucleotide 13224 is replaced by G,
invention 23 to SeqIdNo.8 wherein nucleotide 30497 is replaced by A,
invention 24 to SeqIdNo.9 wherein nucleotide 24811 is replaced by C,
invention 25 to SeqIdNo.9 wherein nucleotide 68280 is replaced by A.

3. Claims: Invention 26: Claim 71 (completely) and claims 51, 52, 70, 72-74 (all partially)

As for invention 2 but limited to SeqIdNo.8 wherein nucleotide 21119 is replaced by A.

4. Claims: Inventions 27-50: claims 75-93 (all partially, as applicable)

A molecule involved in bone modulation that is, binds to or inhibits binding of a molecule to a protein involved in focal adhesion signaling, and applications thereof, wherein invention 27 is limited to a molecule that is, binds to or inhibits binding of a molecule to the protein of SeqIdNo.87 or the corresponding nucleic acid of SeqIdNo.63,
invention 28 to the protein of SeqIdNo.88 or the corresponding nucleic acid of SeqIdNo.64,
invention 29 to the protein of SeqIdNo.89 or the corresponding nucleic acid of SeqIdNo.65,
invention 30 to the protein of SeqIdNo.90 or the corresponding nucleic acid of SeqIdNo.66,
invention 31 to the protein of SeqIdNo.91 or the corresponding nucleic acid of SeqIdNo.67,
invention 32 to the protein of SeqIdNo.92 or the corresponding nucleic acid of SeqIdNo.68,
invention 33 to the protein of SeqIdNo.93 or the corresponding nucleic acid of SeqIdNo.69,
invention 34 to the nucleic acid of SeqIdNo.70,
invention 35 to the protein of SeqIdNo.94 or the corresponding nucleic acid of SeqIdNo.71,
invention 36 to the protein of SeqIdNo.95 or the corresponding nucleic acid of SeqIdNo.72,
invention 37 to the protein of SeqIdNo.96 or the corresponding nucleic acid of SeqIdNo.73,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

invention 38 to the protein of SeqIdNo.97 or the corresponding nucleic acid of SeqIdNo.74,
invention 39 to the protein of SeqIdNo.98 or the corresponding nucleic acid of SeqIdNo.75,
invention 40 to the protein of SeqIdNo.99 or the corresponding nucleic acid of SeqIdNo.76,
invention 41 to the protein of SeqIdNo.100 or the corresponding nucleic acid of SeqIdNo.77,
invention 42 to the protein of SeqIdNo.101 or the corresponding nucleic acid of SeqIdNo.78,
invention 43 to the protein of SeqIdNo.102 or the corresponding nucleic acid of SeqIdNo.79,
invention 44 to the protein of SeqIdNo.103 or the corresponding nucleic acid of SeqIdNo.80,
invention 45 to the protein of SeqIdNo.104 or the corresponding nucleic acid of SeqIdNo.81,
invention 46 to the protein of SeqIdNo.105 or the corresponding nucleic acid of SeqIdNo.82,
invention 47 to the protein of SeqIdNo.106 or the corresponding nucleic acid of SeqIdNo.83,
invention 48 to the protein of SeqIdNo.107 or the corresponding nucleic acid of SeqIdNo.84,
invention 49 to the protein of SeqIdNo.108 or the corresponding nucleic acid of SeqIdNo.85,
invention 50 to the protein of SeqIdNo.109 or the corresponding nucleic acid of SeqIdNo.86.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 43,44

Present claims 43 and 44 relate to a compound defined by reference to a desirable characteristic or property, namely that it binds to the nucleic acid sequence of claim 1. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such compound. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search can be carried out for such speculative claims, the wording of which is a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

I ational Application No

PCT/US 00/16951

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